

Fig. 1

Mutant-specific oligonucleotide primers used for mutant number 1. Mutated nucleotide underlined.

Bet v 1 sense 5'- AATTATGAGACTGAGACCCCCTCTGTTATCCCAGCAGCTCG -3'
Bet v 1 non-sense 3'- TTAATACTCTGACTCTGGTGGAGACAATAGGGTCGTCGAGC -5'
sense primer 5'- TGAGACCCCCTCTGTTATCCCAG -3'
non-sense primer 3'- ATACTCTGACTCTGGGGGAGACA -5'

[illegible]

Fig. 2

Oligonucleotide primers for site directed mutagenesis of
Bet v 1 (No. 2801).

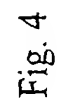
all	sense	1: 183Bv, 15-mer 5'-GTTGCCAACGATCAG
1	sense	2: 184Bv, 23-mer 5'-TGAGACCCCTCTGTATCCCAG
1	non-sense	3: 185Bv, 23-mer 5'-ACAGAGGGGTCTCAGTCTCATA
2	sense	4: 186Bv, 31-mer 5'-GATACCTCTTTCCACAGGTTGCACCCCAAG
2	non-sense	5: 187Bv, 31-mer 5'-ACCTGTGGAAAGAGGGTATCGCCATCAAGGA
3	sense	6: 188Bv, 23-mer 5'-AACATTTTCAGGAAATGGAGGGCC
3	non-sense	7: 189Bv, 23-mer 5'-TTTCCTGAAATGTTTCAACACT
4	sense	8: 190Bv, 23-mer 5'-TTAAGAACATCAGCTTTCCCGAA
4	non-sense	9: 191Bv, 23-mer 5'-AGCTGATGTTCTTAATGGTTCCA
5	sense	10: 192Bv, 23-mer 5'-GGACCATGCAAACTTCAAATACA
5	non-sense	11: 193Bv, 23-mer 5'-AGTTTGCATGGTCCACCTCATCA
6	sense	12: 194Bv, 23-mer 5'-TTTCCTCAGGCCTCCCTTTCAA
6	non-sense	13: 195Bv, 23-mer 5'-AGGCCTGAGGGAAAGCTGATCTT
7	sense	14: 196Bv, 24-mer 5'-TGAAGGATCTGGAGGGCCTGGAAC
7	non-sense	15: 197Bv, 24-mer 5'-CCCTCCAGATCCTTCAATGTTTTTC
8	sense	16: 198Bv, 24-mer 5'-GGCAACTGGTGATGGAGGATCCAT
8	non-sense	17: 199Bv, 24-mer 5'-CCATCACCAGTTGCCACTATCTTT
all	non-sense	18: 200Bv, 15-mer 5'-CATGCCATCCGTAAG

10001245-333504

Fig. 3

Overview of all Bet v 1 mutations

1 (A-C)	
GGTGTGTTTAATTATGAGACTGAGACCACTCTGTTATCCCAGCAGCTCGACTGTTCAAG	60
G V F N Y E T E T T P S V I P A A R L F K	20
9 (A-G) 2 (A-C) 2 (A-C)	
GCCTTTATCCTTGATGGGATAAAGGTTGCACCCCAAGCCATTAGCAGT	120
A F I L D-G G D N-T L F P K-Q V A P Q A I S S	40
3 (GA-TC) 7 (AA-TC) 4 (G-C) 6 (GA-TC)	
GTTGAAACATTGAAGGAAATGGAGGGCCTGGAACCATTAAGAAGATCAGCTTTCCCGAA	180
V E N I E-S G N-S G G P G T I K K-N I S F P E-S	60
5 (CA-TG)	
GGCCTCCCTTTCAAGTACGTGAAGGACAGAGTTGATGAGGTGGACCAACAACCTTCAAA	240
G L P F K Y V K D R V D E V D H T-A N F K	80
TACAATTACAGCGTGATCGAGGGCGTCCCATAGGCGACACATTGGAGAAGATCTCCAAC	300
Y N Y S V I E G G P I G D T L E K I S N	100
10 (GAG-CAC) 8 (CCC-TGG)	
GAGATAAAGATAGTGGCAACCCCTGATGGAGGATCCATCTTGAAGATCAGCAACAAGTAC	360
E I K I V A T P-G D G G S I L K I S N K Y	120
CACACCAAAGGTGACCATGAGGTGAAGGCAGAGCAGGTTAAGGCAAGTAAAGAAATGGGC	420
H T K G D H E V K A E Q V K A S K E M G	140
GAGACACTTTTGAGGGCCGTTGAGAGCTACCTCTTGGCACACTCCGATGCCTACAACATA	480
E T L L R A V E S Y L L A H S D A Y N stop	159



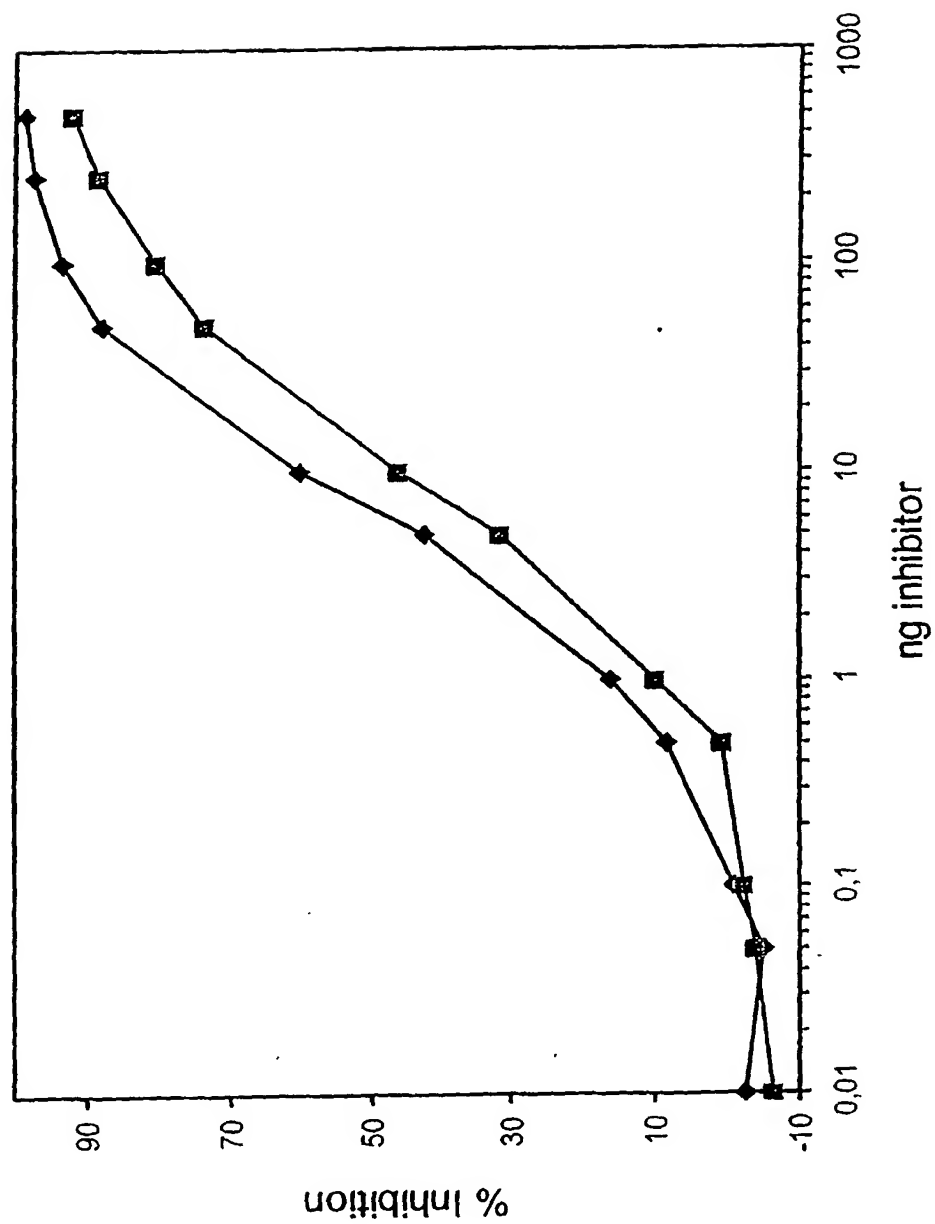


Fig. 5 —◆— Bet v 1 —■— Asn28Thr+Lys32Gln

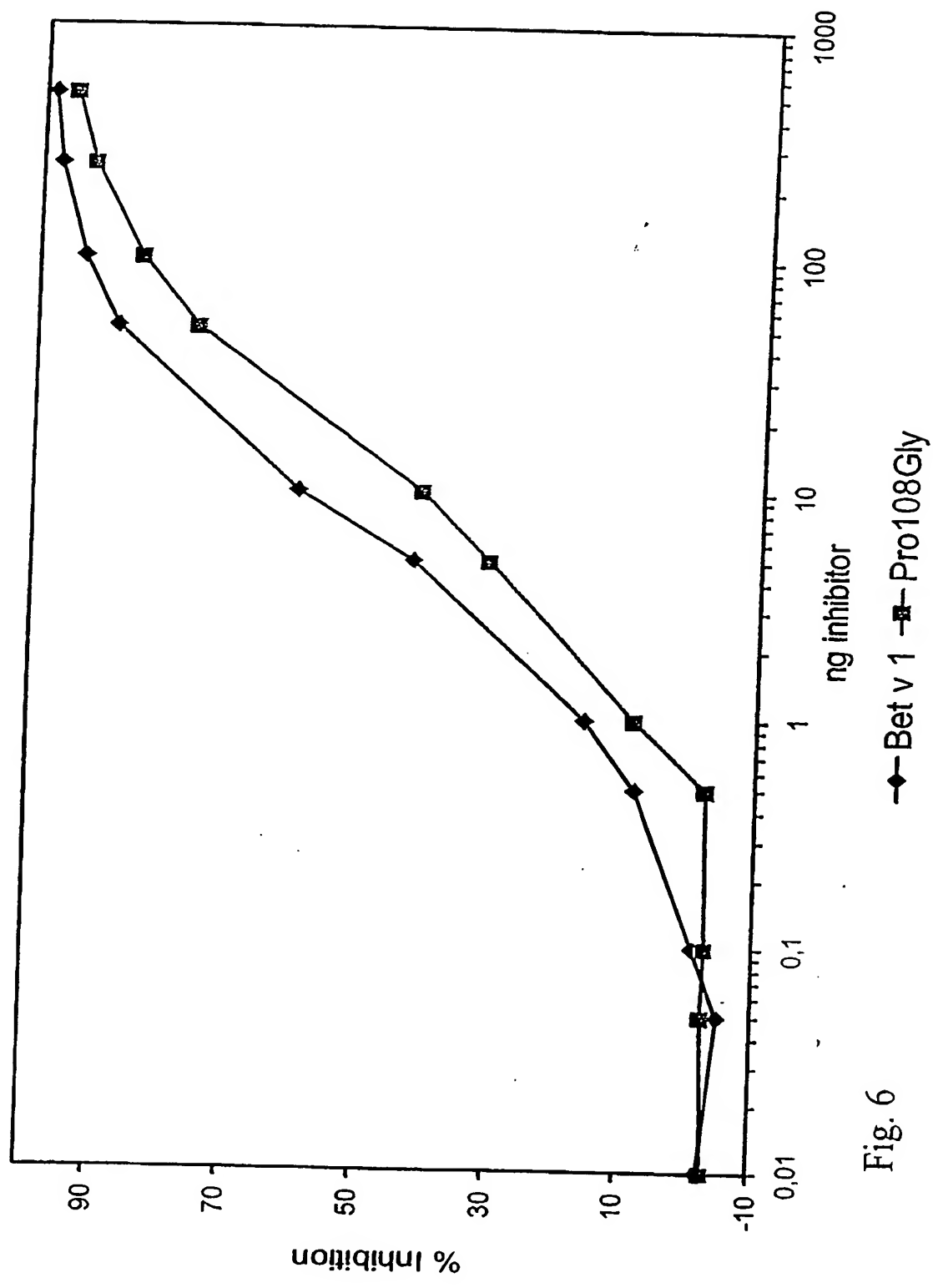
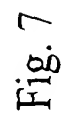


Fig. 6



705111 5427000
 10mM Na2HPO4/NaH2PO4 0.02MNa3N3

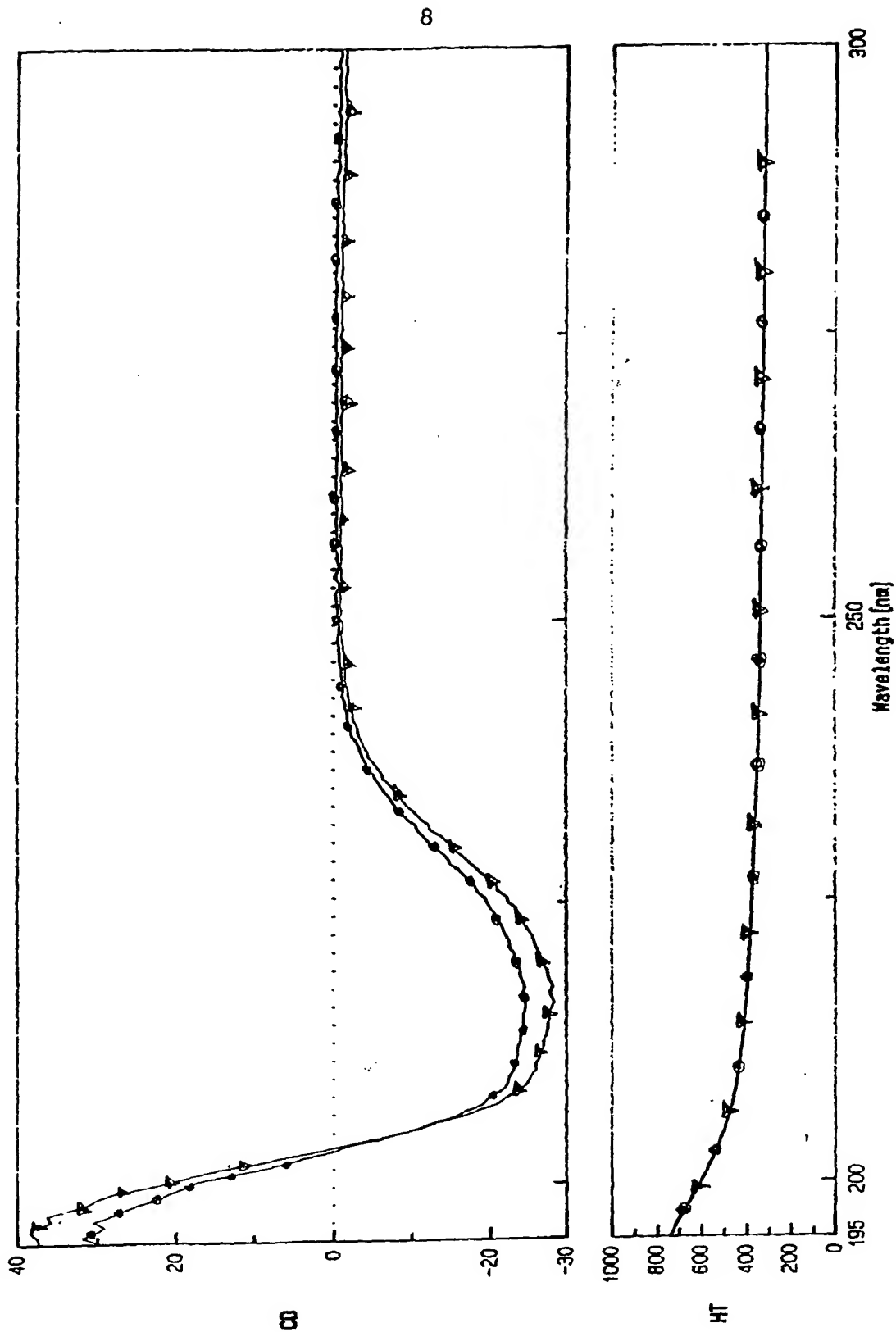
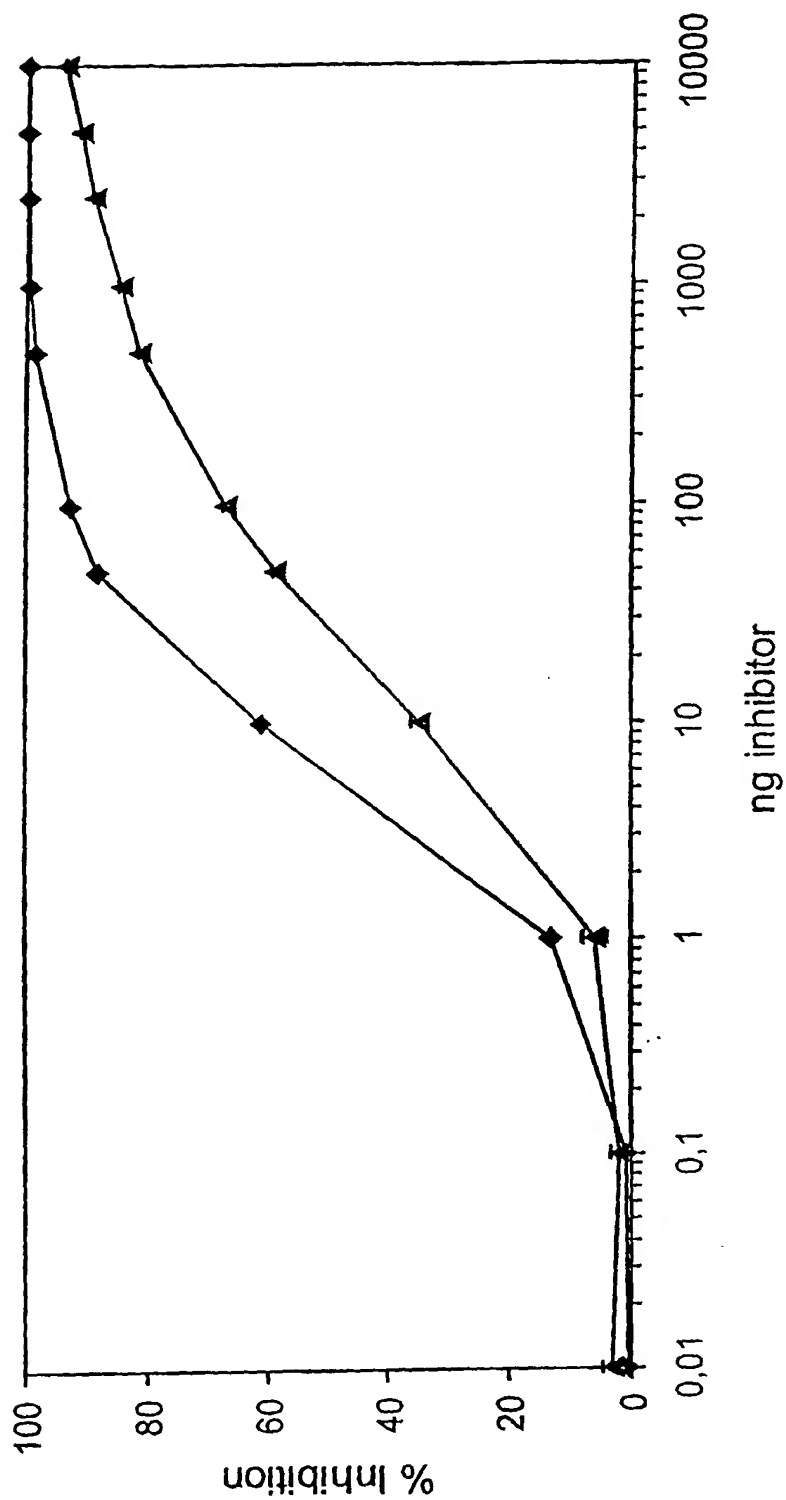


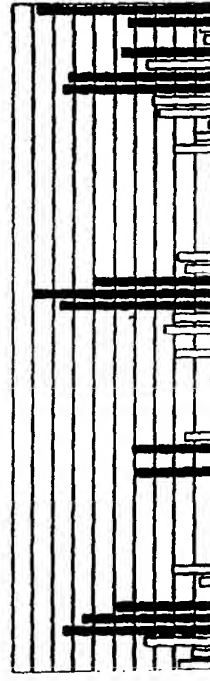
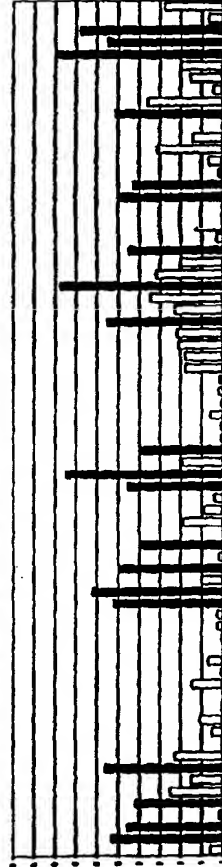
FIG. 8



◆ Bet v 1 ▲ Glu45Ser, Pro108Gly, Asn28Thr+Lys32Gln.

Fig. 9

A large, intricate black and white fractal pattern, resembling a Sierpinski triangle or a similar geometric construction, filling the page. The pattern is composed of many small, repeating geometric shapes, creating a complex, self-similar structure. The overall shape is roughly rectangular, with a jagged, irregular right edge. The pattern is dense and detailed, with many small gaps and voids interspersed among the solid black areas.



A large, complex grid of letters and symbols, resembling a crossword puzzle or a data matrix. The grid is filled with various characters, including letters, numbers, and symbols, arranged in a structured pattern. The grid is oriented vertically, with the text rotated 90 degrees clockwise.

Figure 10.

Mutant-specific oligonucleotide primers used for Ves v 5 mutants.
Mutated nucleotides underlined.

Ves v 5 sense 5'- ACCACAGCCTCCAGCGAAGAATATGAAAAATTTGGTATGGA -3'

Ves v 5 non-sense 3'- TGGTGTCTGGAGGTCGCTTCTTATACTTTTTAAACCATACCT -5'

sense primer 5'- CCAGCGCTAATATGAAAAAT -3'

non-sense primer 3'- GTCGGAGGTCGCGGATTATAC -5'

Ves v 5 sense 5'- GGCTAATCAATGTCAATATGGTCACGATACTTGCAGGGGATG -3'

Ves v 5 non-sense 3'- CCGATTAGTTACAGTTATACCAGTGCTATGAACGTCCCTAC -5'

sense primer 5'- TGTCAAAGCTGGTCACGATACT -3'

non-sense primer 3'- TTAGTTACAGTTCCGACCAGTG -5'

Fig. 12

12

Oligonucleotide primers for site directed mutagenesis of Ves v 5.

all sense 1: XhoI start, 38-mer:

EcoRI
 5'-CCGCTCGAGAAAAGAAACAATTATTGTAAAAATAAAATG
 L E K R N N Y C K I K
 Kex2 cleavage site amino terminus of Ves v 5

1	sense	1: K72As	21-mer	5'-CCAGCGGCTAATATGAAAAAT
1	non-sense	2: K72Aa	21-mer	5'-CATATTAGCCGCTGGAGGCTG
2	sense	3: Y96As	21-mer	5'-TGTCAAGCTGGTCACGATACT
2	non-sense	4: Y96Aa	21-mer	5'-GTGACCAGCTTGACATTGATT
all non-sense 7: CT-pPICZαA, 21-mer				5'-ATTCATCAGCTGCGAGATAGG

100145-1153

Fig. 13

13

Overview of Ves v 5 mutations

1	AACAATTATTGTAAAATAAAATGTTTGAAAGGAGGTGTCCATACTGCCTGCAAATATGGA	60
1	N N Y C K I K C L K G G V H T A C K Y G	20
61	AGTCTTAAACCGAATTGCGGTAATAAGGTAGTGGTATCCTATGGTCTAACGAAACAAGAG	120
21	S L K P N C G N K V V V S Y G L T K Q E	40
121	AAACAAGACATCTTAAAGGAGCACAATGACTTTAGACAAAAAATTGCACGAGGATTGGAG	180
41	K Q D I L K E H N D F R Q K I A R G L E	60
	1 [K72A] (AAG-GCT)	
181	ACTAGAGGTAATCCTGGACCACAGCCTCCAGCGAAGAATATGAAAAATTGGTATGGAAC	240
61	T R G N P G P Q P P A K N M K N L V W N	80
	2 [Y96A] (TA-GC)	
241	GACGAGTTAGCTTATGTGCGCCCAAGTGTGGGCTAATCAATGTCAATATGGTCACGATACT	300
81	D E L A Y V A Q V W A N Q C Q Y G H D T	100
301	TGCAGGGATGTAGCAAAATATCAGGTTGGACAAAACGTAGCCTTAACAGGTAGCACGGCT	360
101	C R D V A K Y Q V G Q N V A L T G S T A	120
361	GCTAAATACGATGATCCAGTTAACTAGTTAAATGTGGGAAGATGAAGTGAAAGATTAT	420
121	A K Y D D P V K L V K M W E D E V K D Y	140
421	AATCCTAAGAAAAAGTTTTTCGGGAAACGACTTTCTGAAAACCGGCCATTACACTCAAATG	480
141	N P K K K F S G N D F L K T G H Y T Q M	160
481	GTTTGGGCTAACACCAAGGAAGTTGGTTGTGGAAGTATAAAATACATTCAAGAGAAATGG	540
161	V W A N T K E V G C G S I K Y I Q E K W	180
541	CACAAACATTACCTTGTATGTAATTATGGACCCAGCGGAAACTTTAAGAATGAGGAACTT	600
181	H K H Y L V C N Y G P S G N F K N E E L	200
601	TATCAAACAAAGTAA	612
201	Y Q T K stop	204

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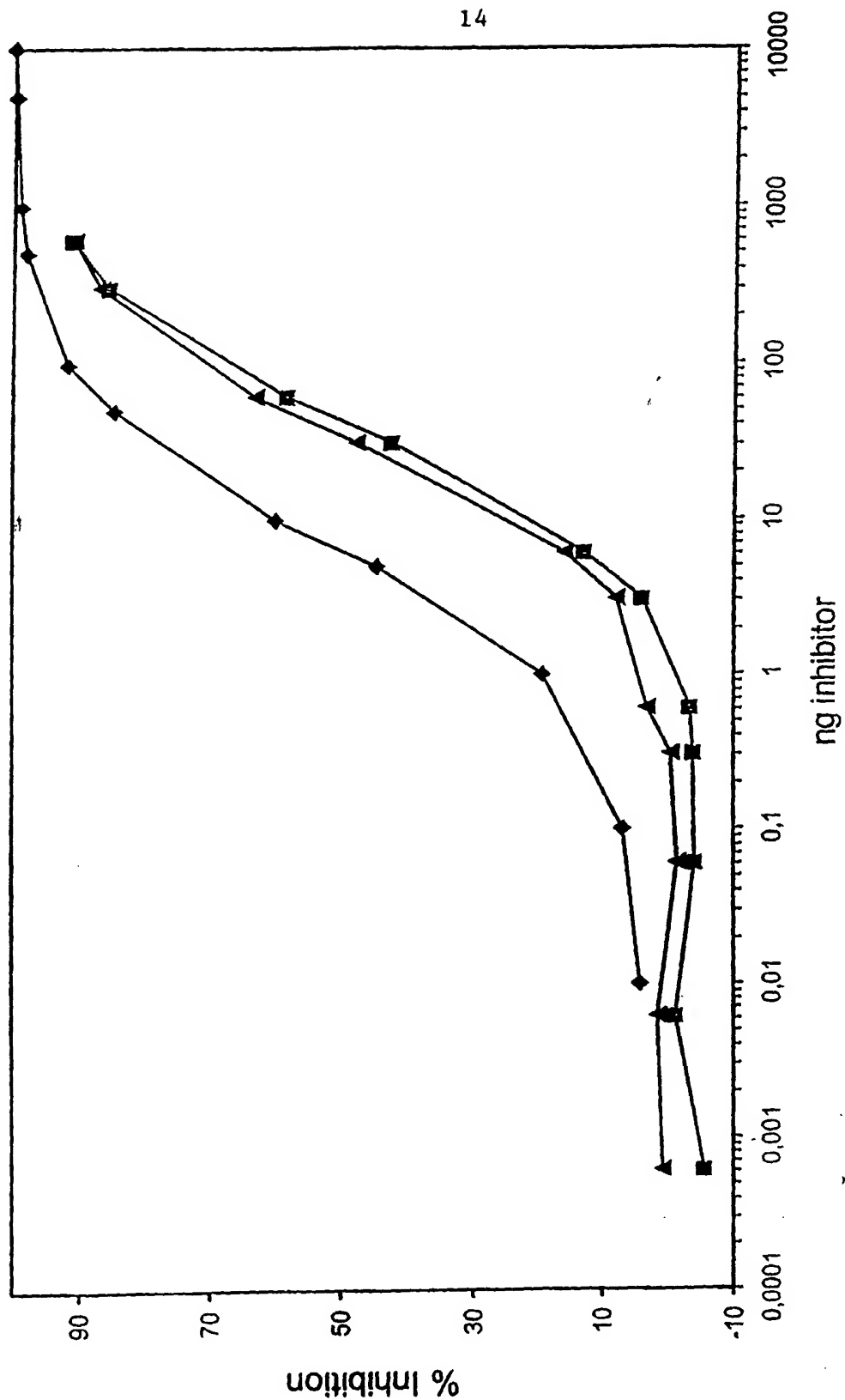
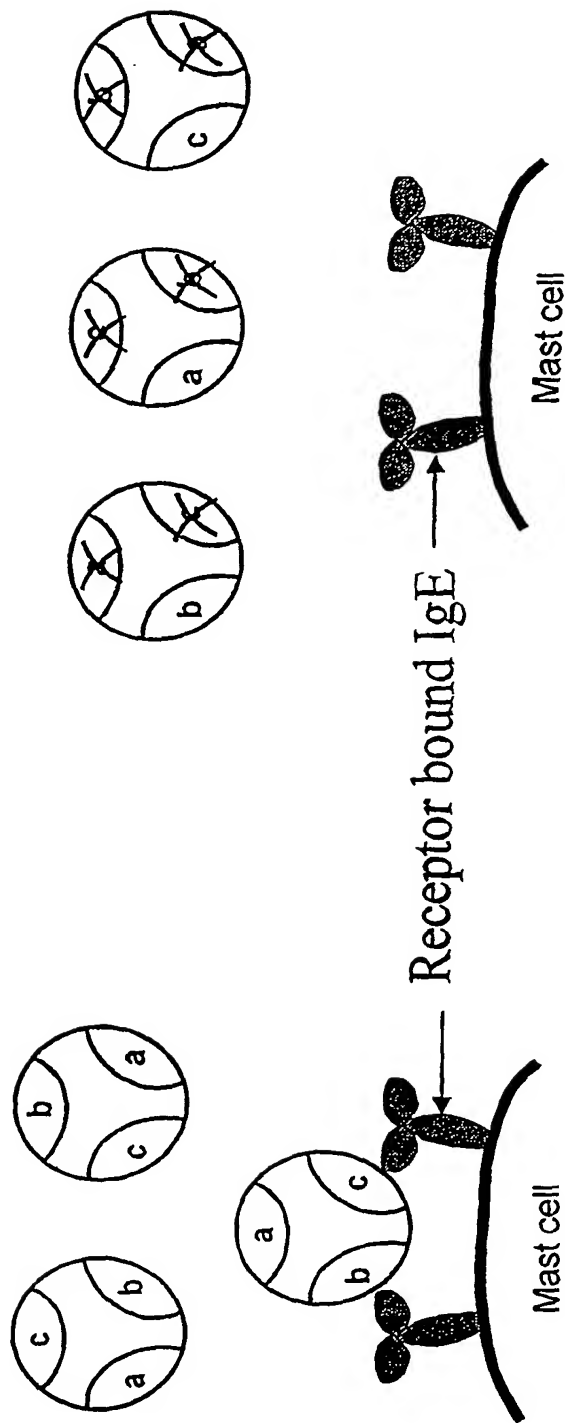


Fig. 14

Fig. 15

Effect of point mutations in dominating IgE epitopes
hypothetical model with 3 epitopes



Cross-linking

Fig. 15A

No cross-linking

Fig. 15B

Fig. 16

DNA SEQUENCE

Der p 2 (DNA sequence referred to in notes in accession No. P49278 SWISSPROT)

ORIGIN

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1   cacaaattct tctttcttc ttactactga tcattaatct gaaaacaaaa ccaaacaac
61  cattcaaaat gatgtacaaa atttgtgtc ttcatgtt ggtcgcagcc gttgctcgtg
121 atcaagtcga tgcataagat tgtgccaatc atgaaatcaa aaaagtttg gtaccaggat
181 gccatggtc agaaccatgt atcattcatc gtggtaaacc attccaatg gaagccgtt
241 tcgaagccaa ccaaaacaca aaaacggcta aaattgaaat caaagcctca atcgatggtt
301 tagaagtga tgttcccggt atcgatccaa atgcatgcca ttacatgaaa tgccattgg
361 ttaaaggaca acaatatgat attaaatata catggaatgt tccgaaaatt gcaccaaaat
421 ctgaaaatgt tgcgtcact gftaaagtta tgggtgatga tgggttttg gcctgtgcta
481 ttgtactca tgctaaaatc cgcgattaaa tcaaacaaaa ttattgatt ttgtaatcac
541 aaatgattga ttttcttcc aaaaaaaaaa taaataaaat ttgggaatt c

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AMINO ACID SEQUENCE

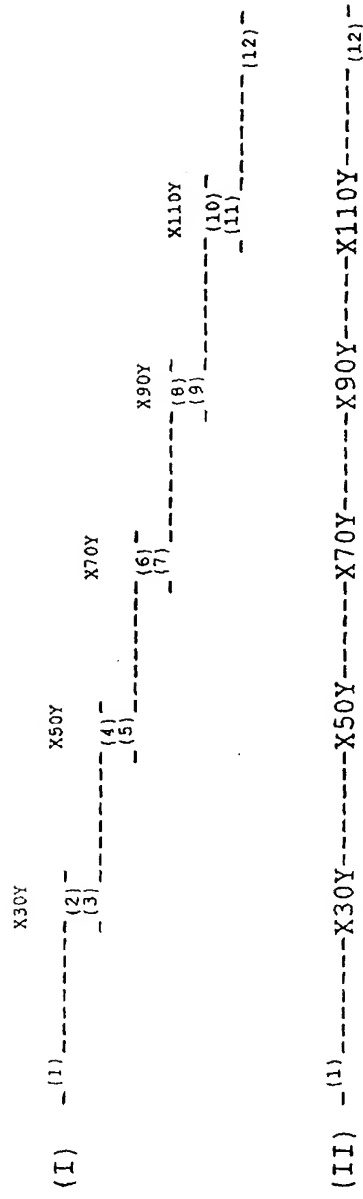
Der p 2 (Accession No. P49278 SWISSPROT; includes signal peptide 1-17)

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1   mmykilclsl lvaavardqv dvkdcanhei kkvlvpgchg sepcihrhk pfqleavfea
61  nqntktakie ikasidglev dvpgidpnac hymkcplvkg qqydikytwn vpkiaapksen
121 vvvtkvmgd dgvlacaiat hakird

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Figure 17



Lines represents DNA sequences.

Numbers in parentheses above lines represents sense oligonucleotide primers: (1), (3), (5), (7), (9), (11).
 Numbers in parentheses below lines represents anti-sense oligonucleotide primers: (2), (4), (6), (8), (10), (12).
 Notation X (position) Y represents mutations.

(1) Represents the sense oligonucleotide primer accommodating the protein N-terminus.

(12) Represents the anti-sense oligonucleotide primer accommodating the protein C-terminus.

Figure 18

Figure 18

Bet v 1 (2637)

Bet v 1 (2628) (Y5V, E45S, K65N, K97S, K134E)

(A16P, N28T, K32Q, K103T, P108G, L152K, A153G, S155P)

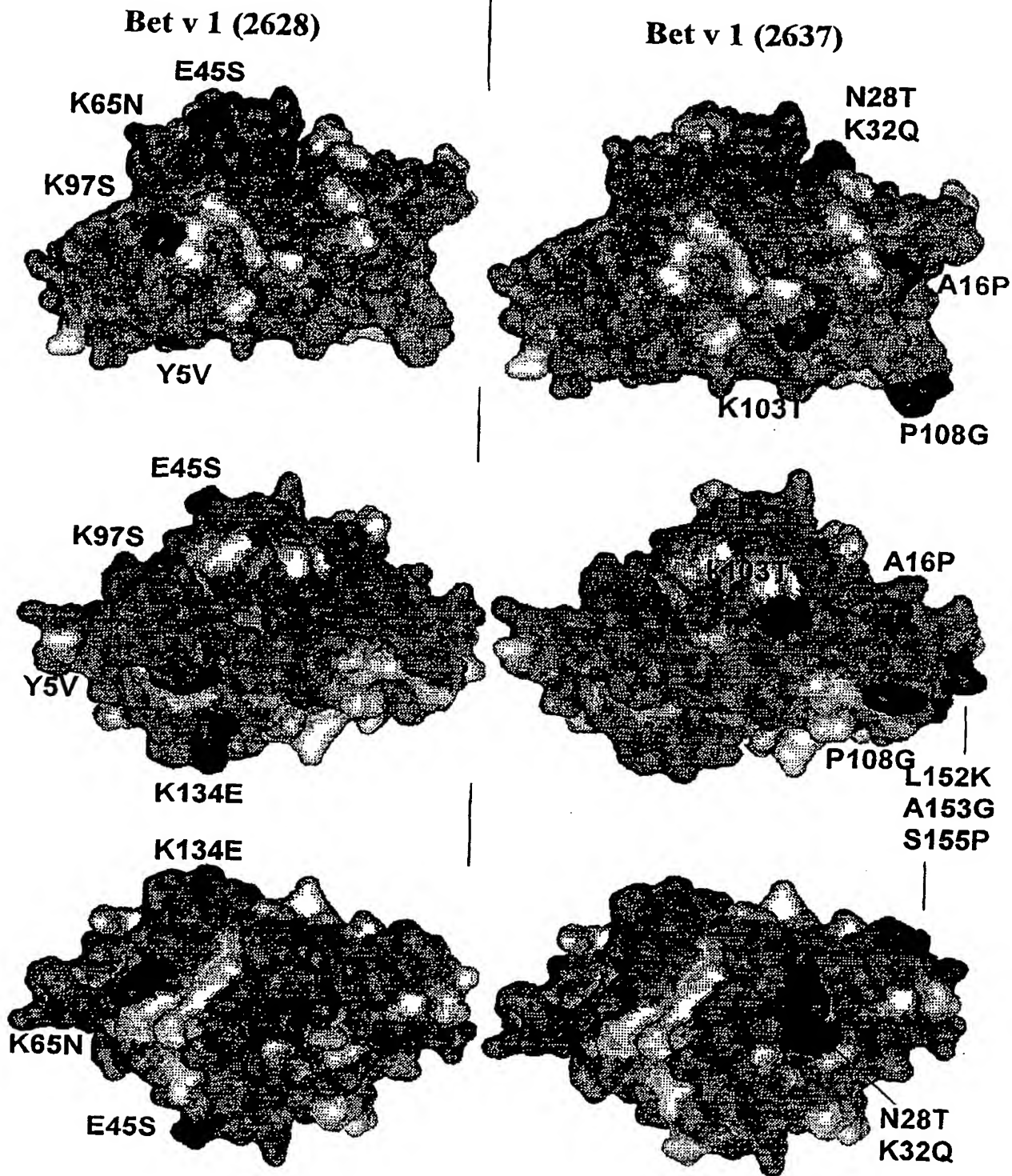
DNA template: Bet v 1 (2589) carrying the Y5V mutation.

DNA template: Bet v 1 (2571) carrying N28T, K32Q, P108G mutations.

331pMalc (s) 189BV (a) 362BV (a) 364BV (a) 366BV (a) 332pMalc (a)
 188BV (s) 361BV (s) 363BV (s) 365BV (s)

331pMalc 368BVa 370BVa 372BVa
 367BVa 369BVa
 331pMalc : CAGACTAATTCGACGTCGGTACCC
 368BVa : CAGTCGcggtGCTGGGATAACAGA
 367BVa : CCAGCACcgCGACTGTTCAAGGCC
 370BVa : CACTATggtTATCTCGTTGGAGAT
 369BVa : GAGATAaccATAGTGGCAActggT
 372BVa: TTACTGATTCATTAGTTGTAGGCATCcggtGTGgcctttGAGGTA

331pMal c : CAGACTAATTCGAGCTCGGTACCC
 189BV : TTTCCTGAAATGTTTCAACACT
 188BV : AACATTCAGGAAATGGAGGGCC
 362Bva : CACGTAGTTGAAAGGGAGGCCTTC
 361BVa : TTTCAACTACGTGAAGGACAGAGT
 364Bva : GGAGATGCTCTCCAATGTGTGCGCC
 363BVa : GGAGAGCATCTCCAACGAGATAAA
 366Bva : ACTTGCTTCAACCTGCTCTGCCTT
 365BVa : CAGGTTGAAGCAAGTAAAGAAATG
 332pMal c : GCAGGTCGACTCTAGAGGATCCAT



Molecular surface of Bet v 1.

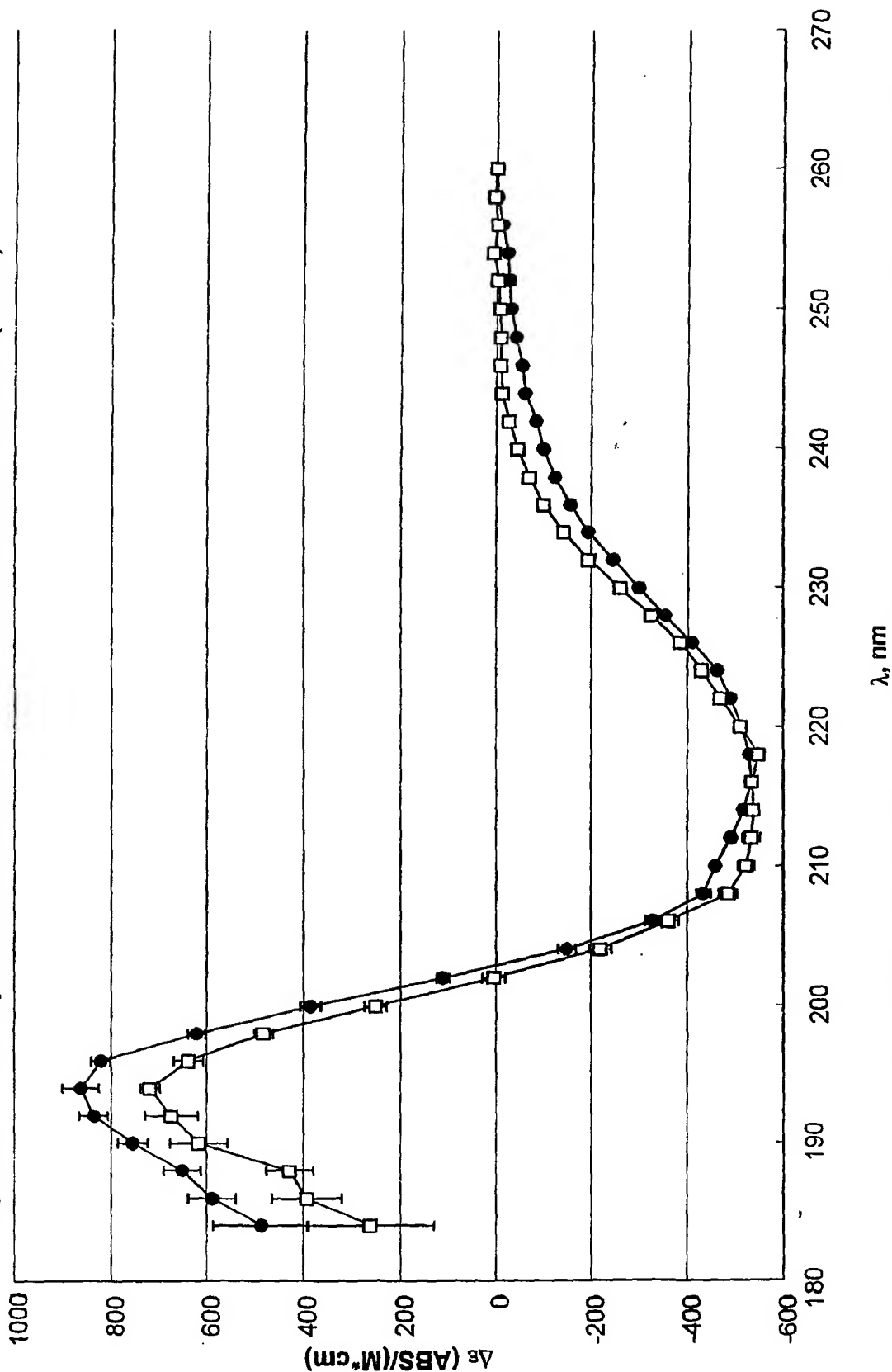
Left side: Bet v 1 (2628), Right side: Bet v 1 (2637)

Grey: Backbone + amino acids 95-100% conserved among *Fagales*

Black: Introduced point mutations.

Figure 19

Figure 20 CD-spectrum of Bet v 1.2801, and mutant Bet v 1 (2637)



CD-spectrum of Bet v 1 (2637), open squares, and the CD-spectrum of native folded Bet v 1.2801, closed circles, both obtained at 20 °C

**Inhibition of human serum IgE-binding to Bet v 1.2801
with Bet v 1.2801 and mutated Bet v 1 allergens**

Figure 21

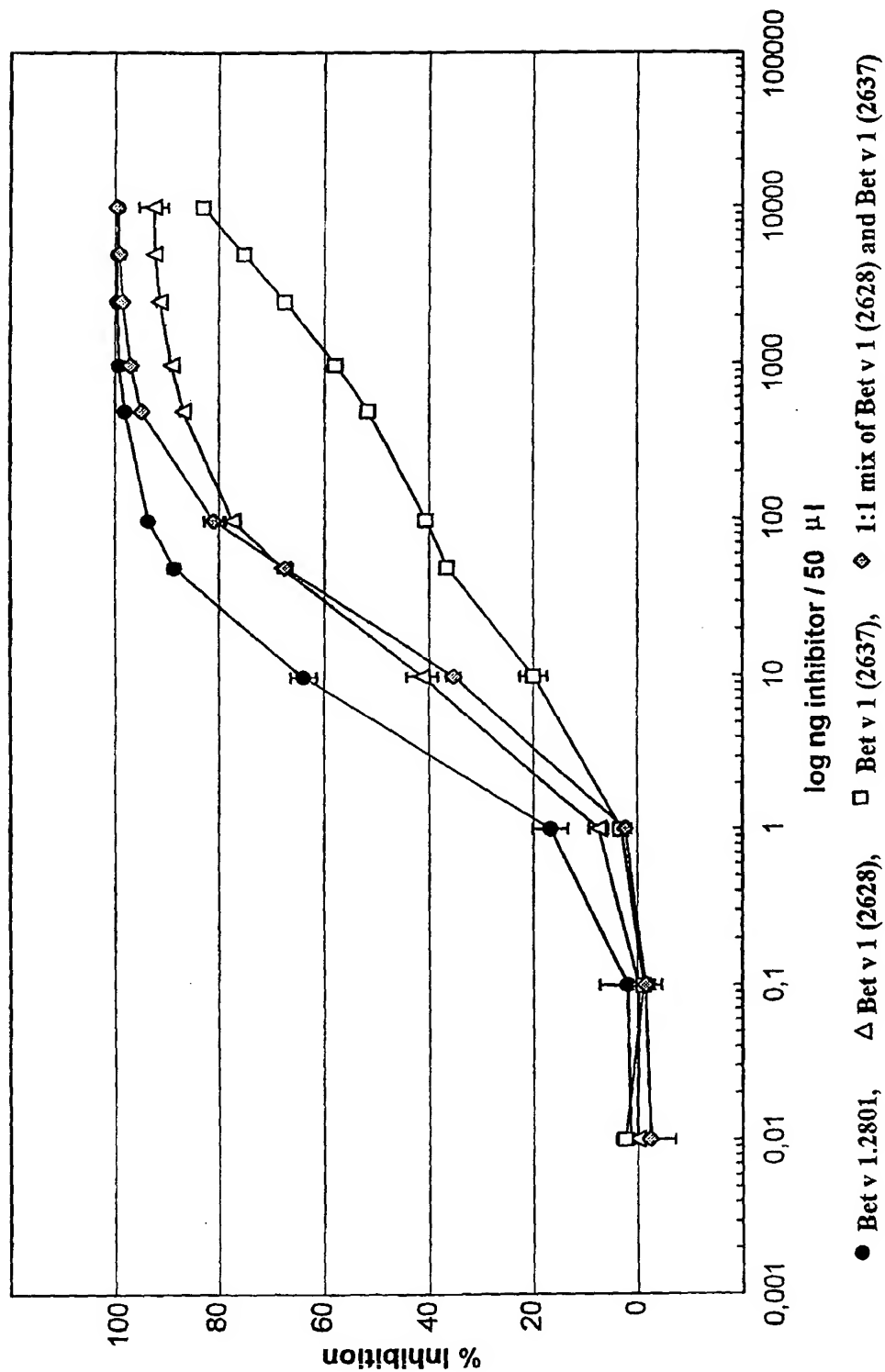


Figure 22 Histamine release, donor MCDS, Bet v 1.2801, Bet v 1(2628), Bet v 1 (2637)

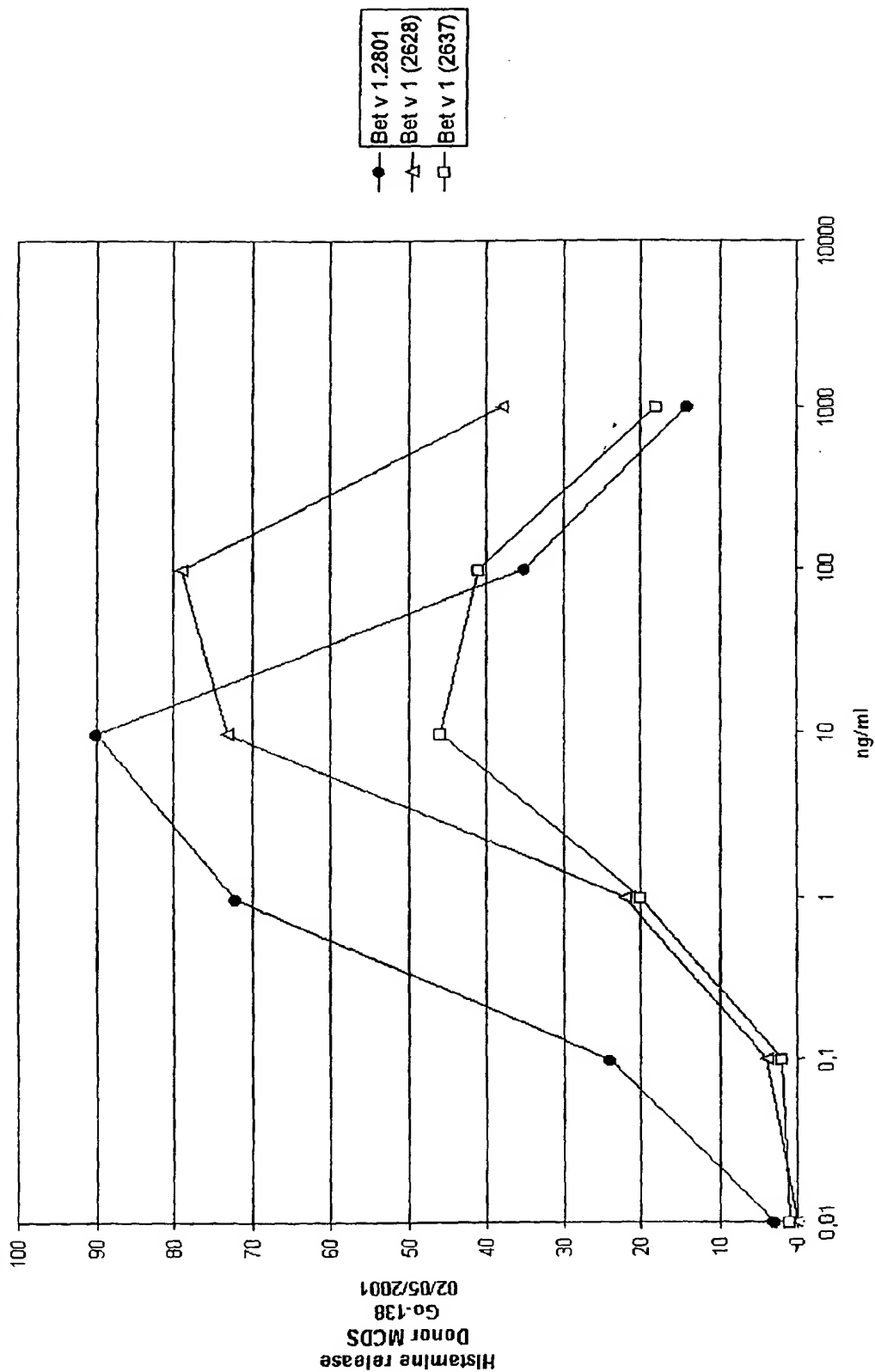


Figure 23 Histamine release, donor MDH, Bet v 1.2801, Bet v 1(2628), Bet v 1 (2637)

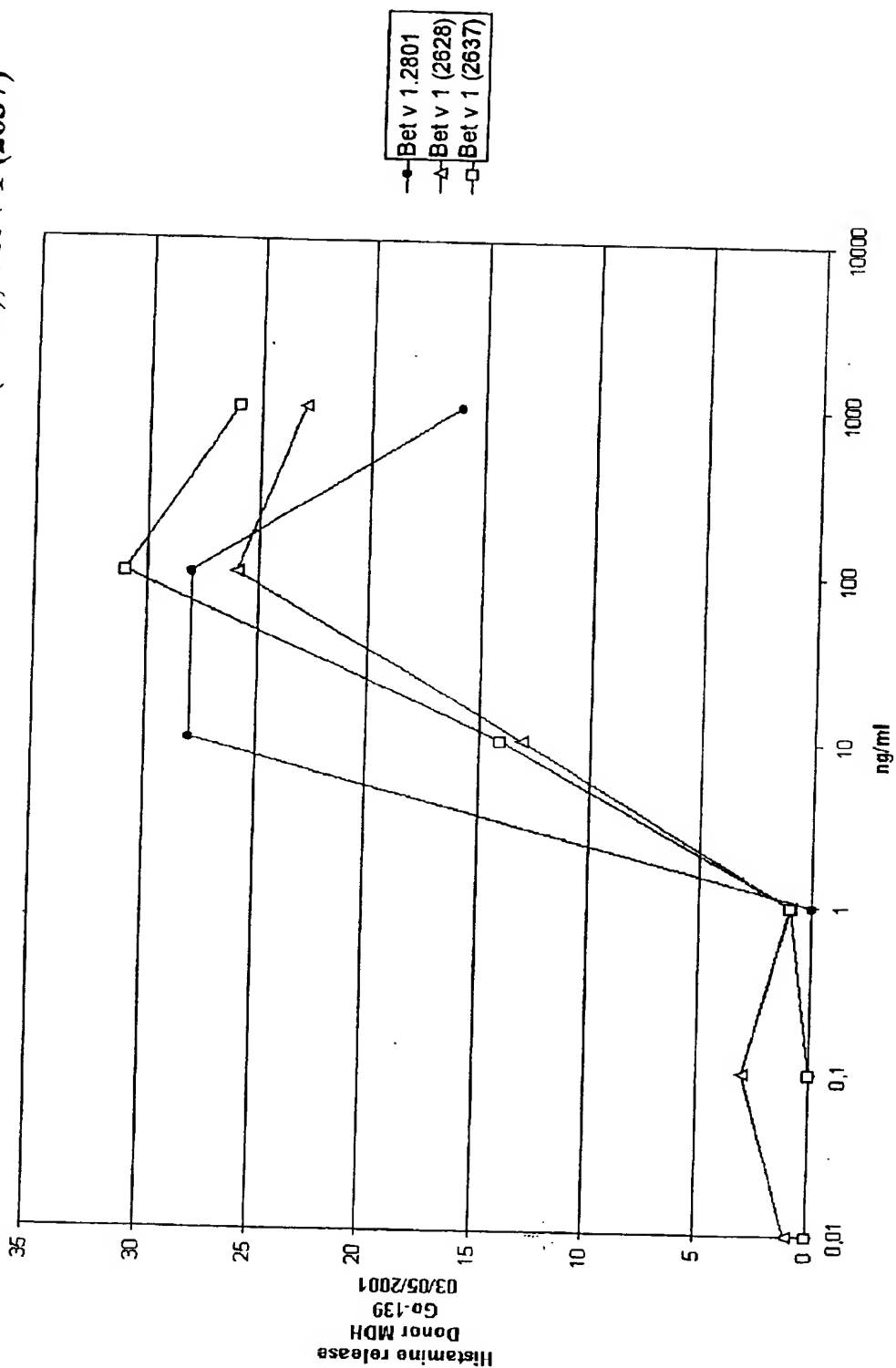
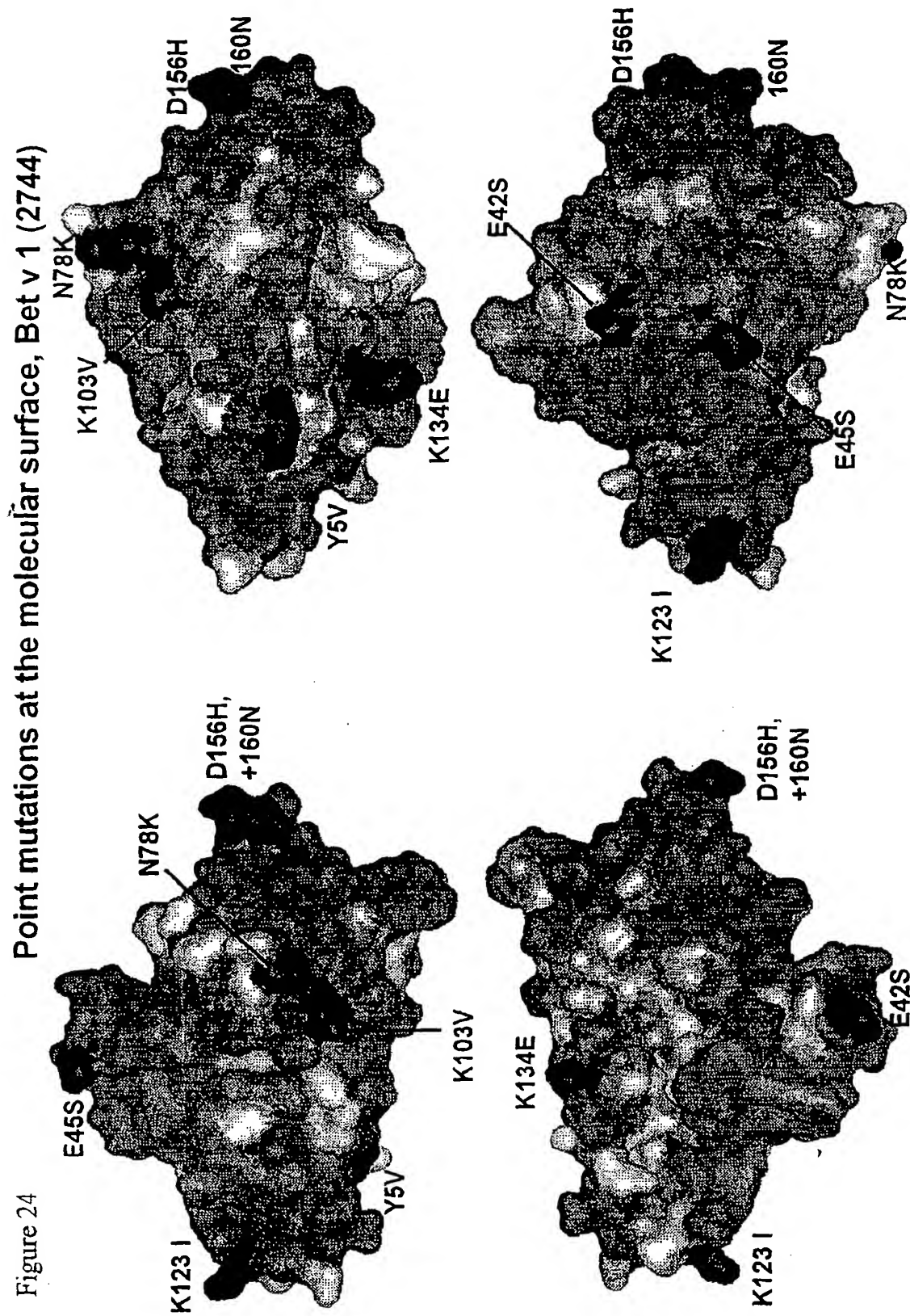
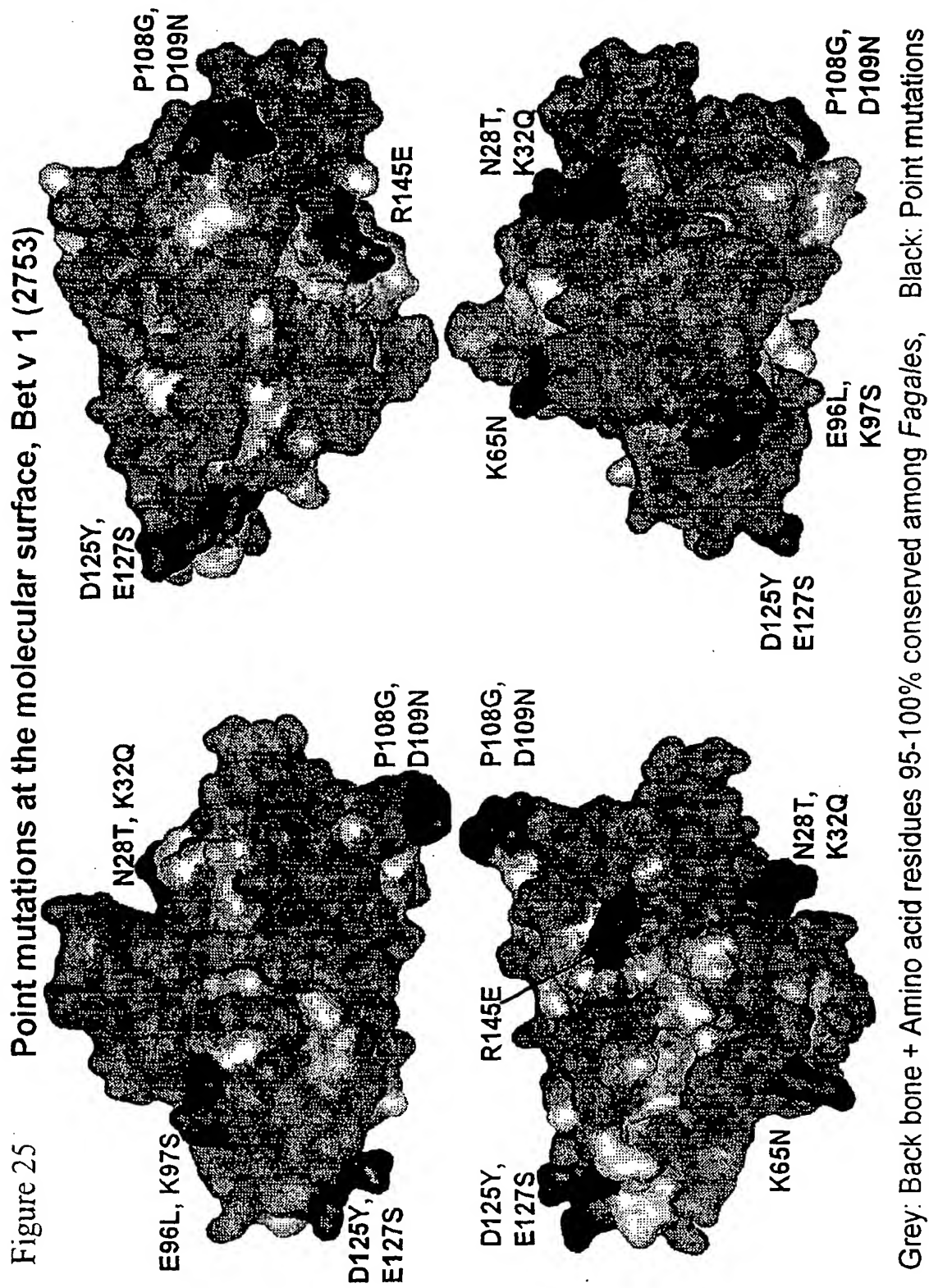
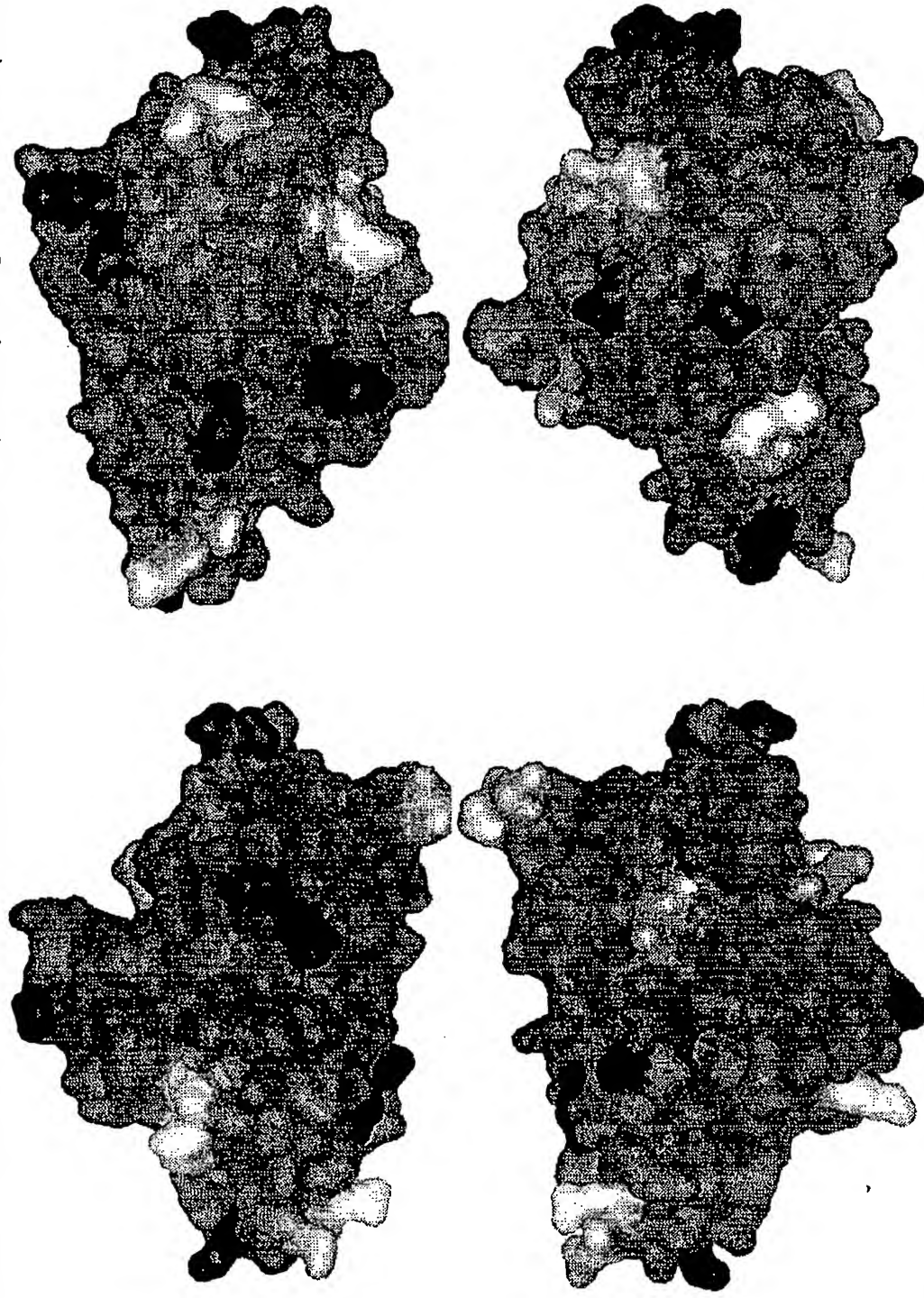


Figure 24





Distribution of point mutations at the molecular surface of, Bet v 1 (2744) [white], and Bet v 1 (2753) [Black]



Grey: Molecular surface; amino acid residues 95-100% conserved among *Fagales*
 Black: Mutations (Y5V, K134E), (E42S, E45S), (N78K, K103V), K123 I, (D156H, +160N)
 White: Mutations (N28T, K32Q), K65N, (E96L, K97S), (P108G, D109N), (D125Y, E127S), R145E

Figure 26

Figure 27 Circular dichroism spectra of Bet v 1.2801 and mutant Bet v 1(2744), pH 7.13, T 20C.

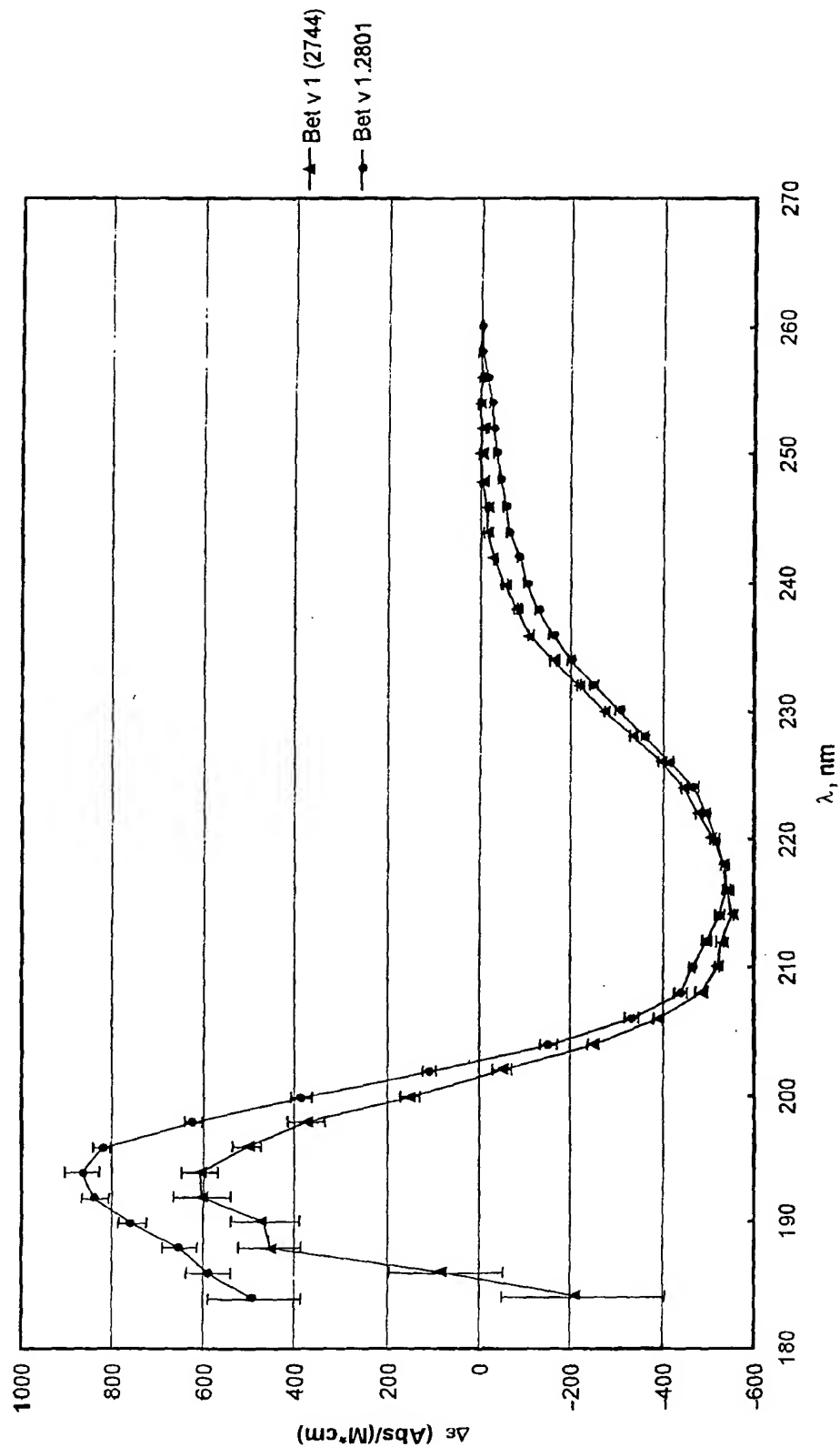


Fig. 28: Histamine release, donor MK, Bet v 1.2801 and Bet v 1(2744)

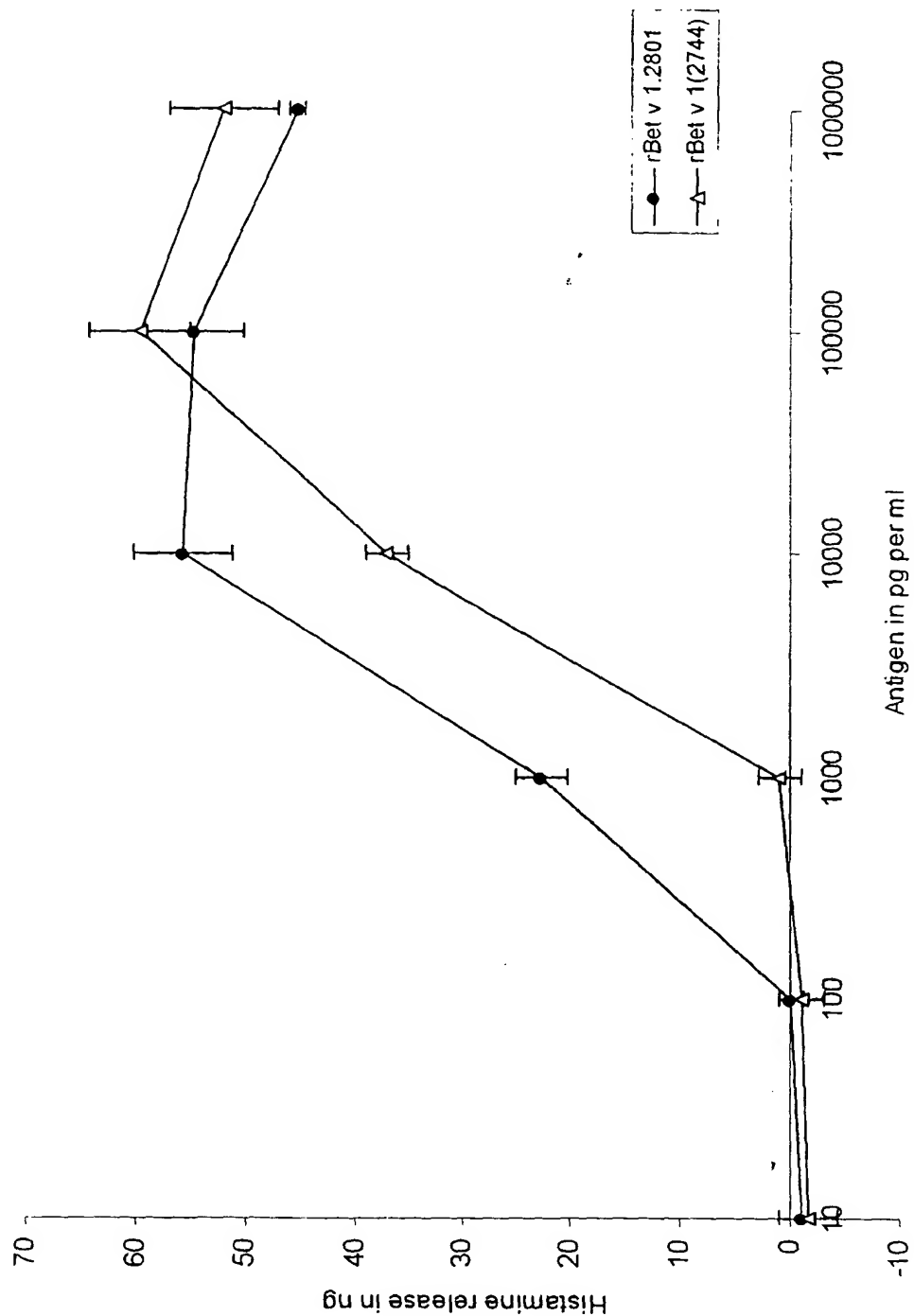


Fig. 29A: Histamine release, donor MJ, Bet v 1.2801 and Bet v 1 (2744)

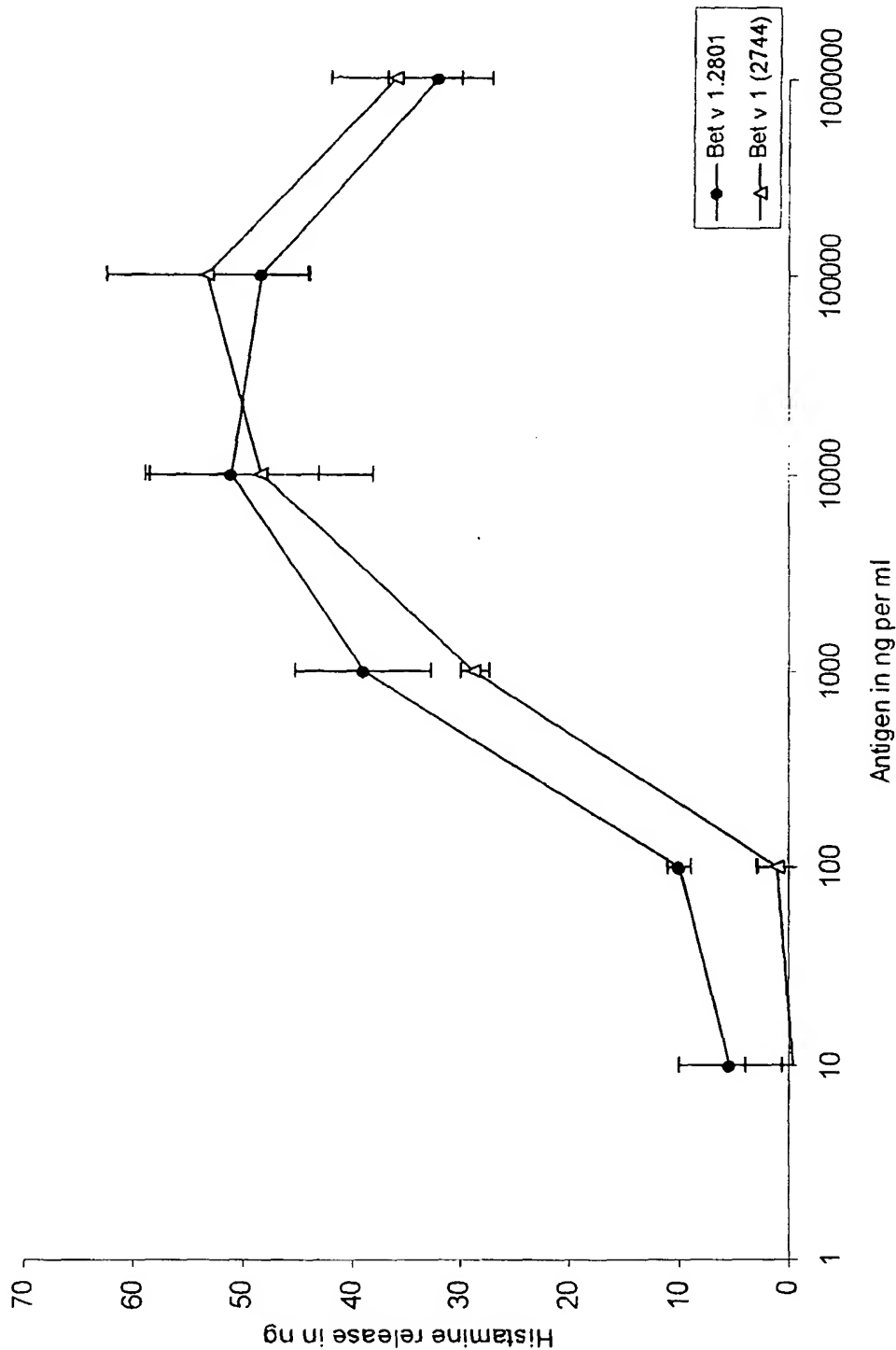


Fig.29B: Histamine release, donor MH, Bet v 1.2801 and Bet v 1 (2744)

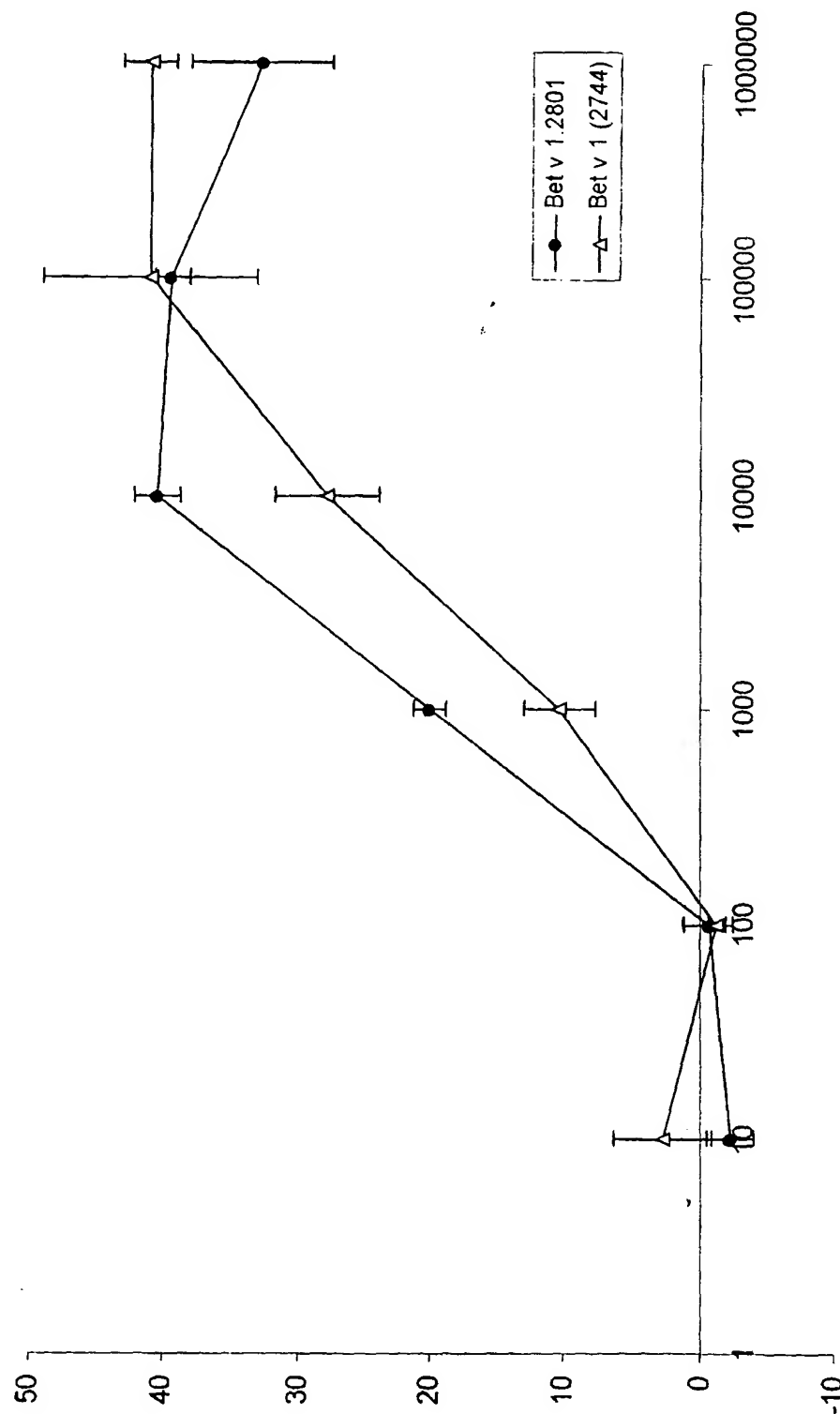


Fig. 29C: Histamine release, donor CJB, Bet v 1.2801 and Bet v 1 (2744)

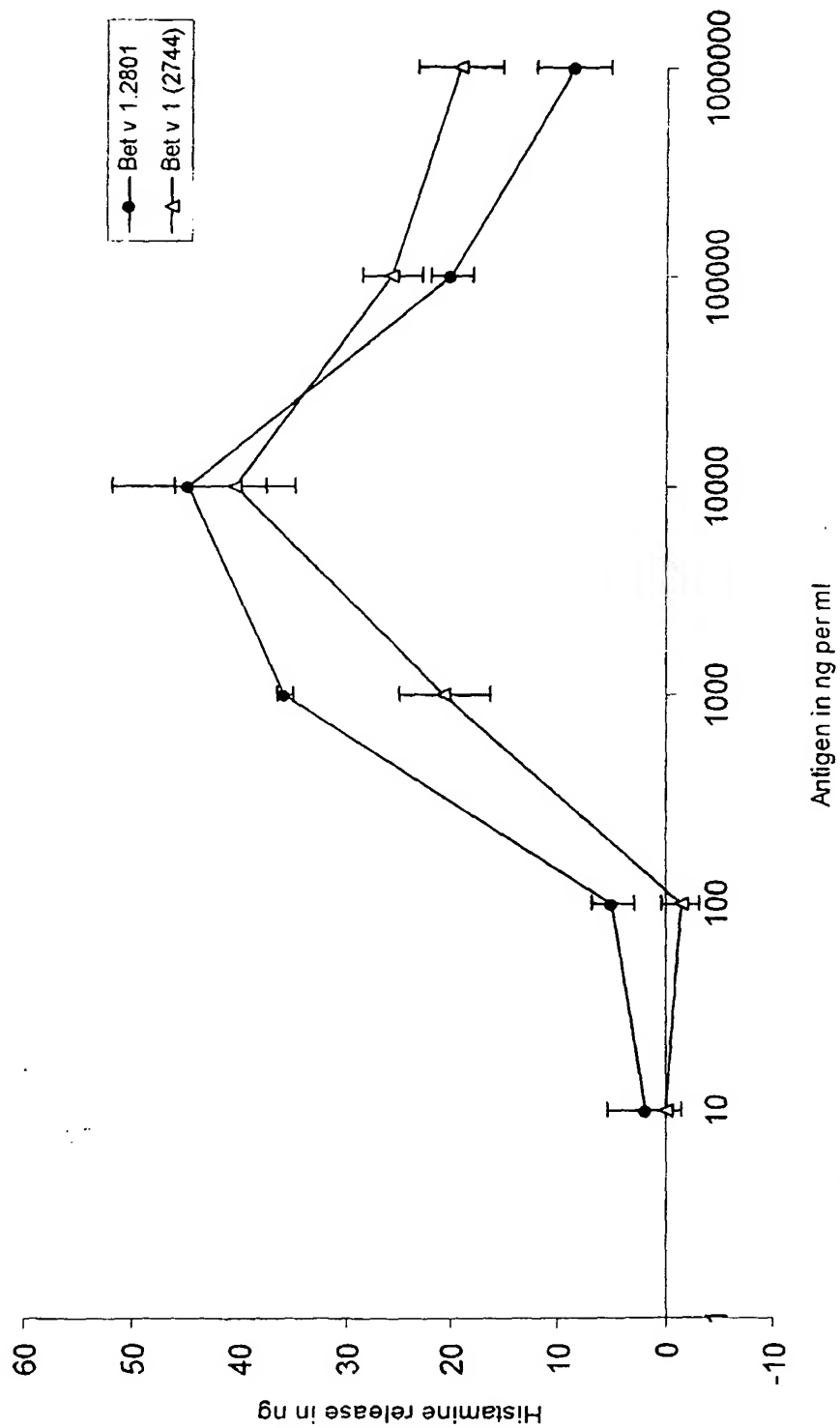


Fig. 29D: Histamine release, donor MCDS, Bet v 1.2801 and Bet v 1 (2744)

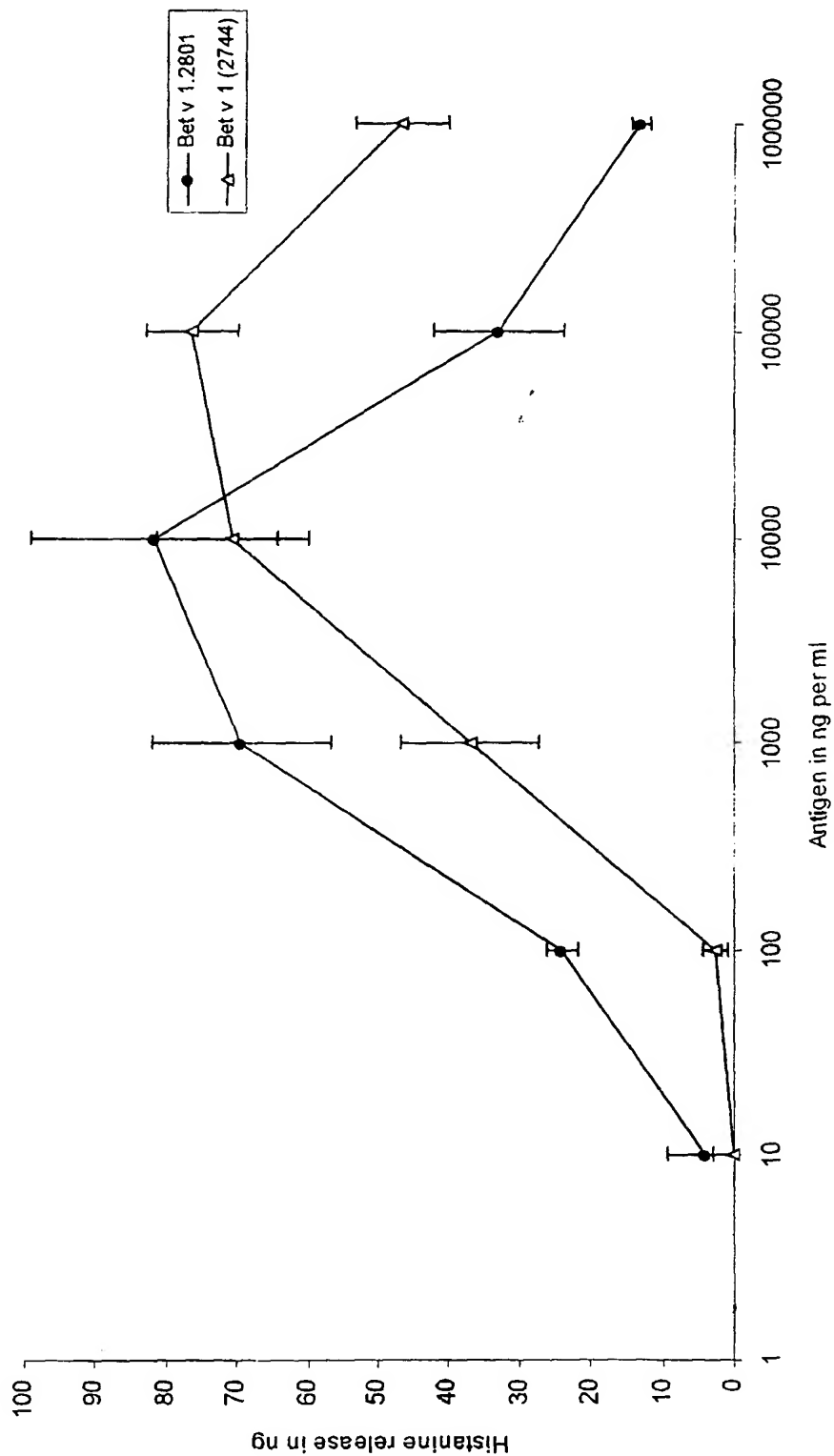
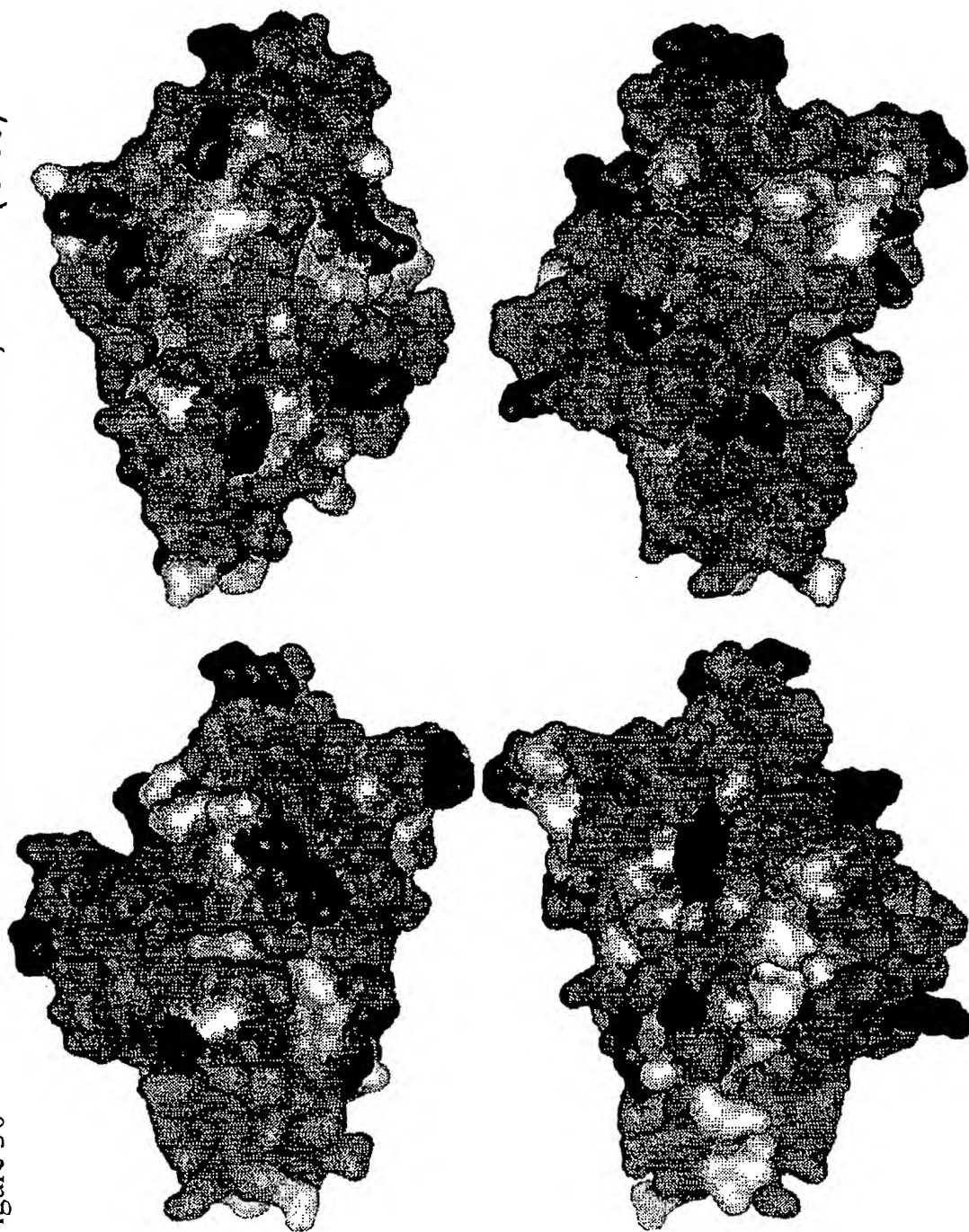


Figure 30 Point mutations at the Molecular surface, Bet v 1 (2733)



Grey: Back bone + Amino acid residues 95-100% conserved among *Fagales*,
Black: Point mutations: Y5V, N28T, K32Q, E45S, K65N, N78K, K97S, K103V, P108G, K134E, R145E, D156H, +160N

Figure 31

Oligonucleotide primers for site-directed mutagenesis of Der p 2

K6A	sense	OB43	42-mer	5' -CCGCTCGAGAAAAGAGATCAAGTCGATGTCGCCGATTGTGCC- 3'
	anti-sense	OB28	39-mer	5' -CGTTCCTAGACTATTAATCGCGGATTTTAGCATGAGTTGC- 3'
K15E	sense	OB44	67-mer	5' -CCGCTCGAGAAAAGAGATCAAGTCGATGTCAAAGATTGTGCC AACCATGAAATCAAAGAAGTTTGG- 3'
	anti-sense	OB28	39-mer	5' -CGTTCCTAGACTATTAATCGCGGATTTTAGCATGAGTTGC- 3'
H30N	sense	OB46	54-mer	5' -CGGGGTACCAGGATGTCATGGTTCAGAACCATGTATCATTAA CCGTGGTAAACC- 3'
	anti-sense	OB28	39-mer	5' -CGTTCCTAGACTATTAATCGCGGATTTTAGCATGAGTTGC- 3'
E62S	sense	OB47	33-mer	5' -GCCTCAATCGATGGTTTATCAGTTGATGTTCCC- 3'
	anti-sense	OB48	33-mer	5' -GGGAACATCAACTGATAAACCATCGATTGAGGC- 3'
H74N	sense	OB49	32-mer	5' -CATGGCATGCAATTACATGAAATGCCCATTTGG- 3'
	anti-sense	OB28	39-mer	5' -CGTTCCTAGACTATTAATCGCGGATTTTAGCATGAGTTGC- 3'
K82N	sense	OB50	50-mer	5' -CTACGCATGCCATTACATGAAATGCCCATTTGGTTAATGGACAA CAATATG- 3'
	anti-sense	OB28	39-mer	5' -CGTTCCTAGACTATTAATCGCGGATTTTAGCATGAGTTGC- 3'

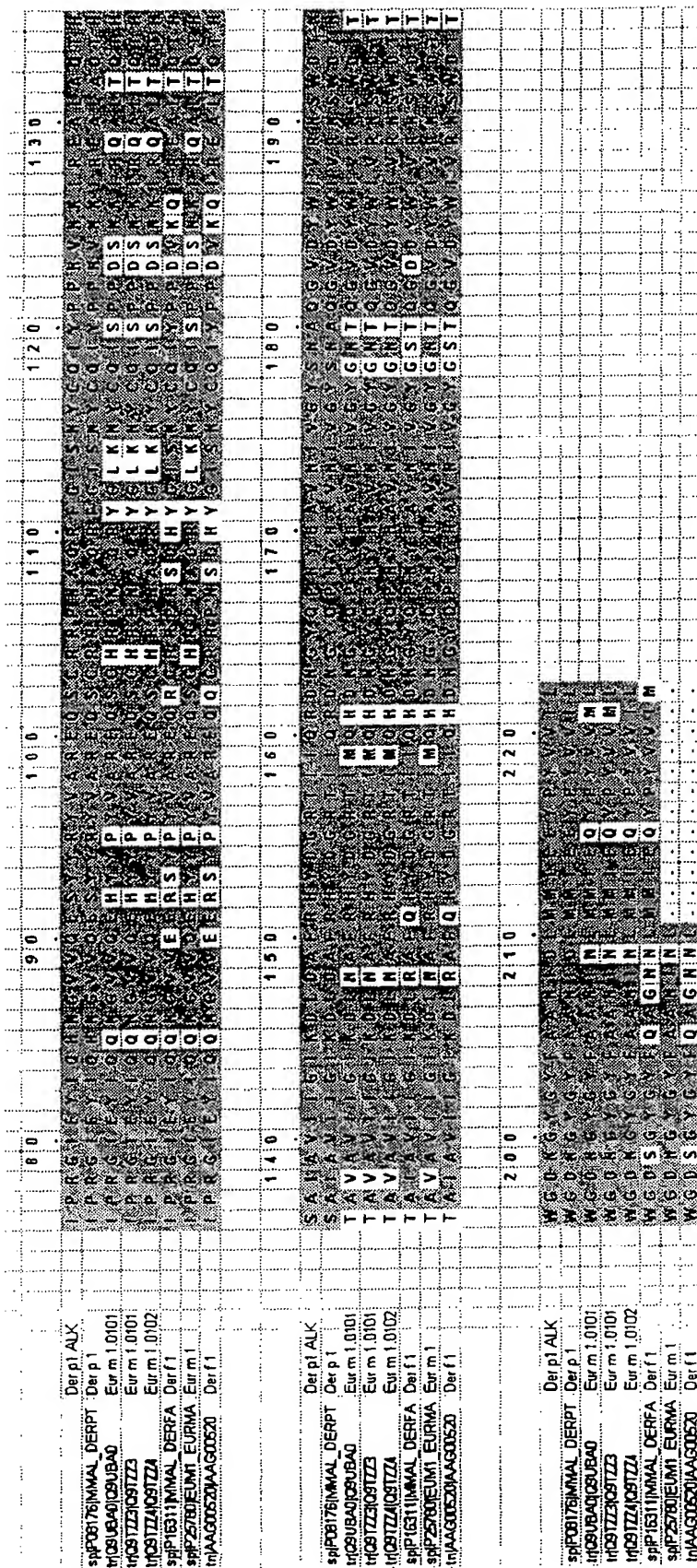
Figure 32 (Der p 2)

[illegible]

The image consists of four separate panels, each displaying a different perspective of a single, highly irregular and textured object. The object appears to be a complex, three-dimensional structure, possibly a biological specimen like a microorganism or a mineral sample. The surface is covered in a dense, granular texture with numerous small protrusions, indentations, and sharp edges. The rendering is in a high-contrast, black and white, halftone style, which emphasizes the rough, uneven nature of the surface. The four panels are arranged in a 2x2 grid, showing the object from various angles to provide a comprehensive view of its morphology.

FIG. 34: Der p 2 mutant

Figure 35B (Der p 1)



10001245 113501

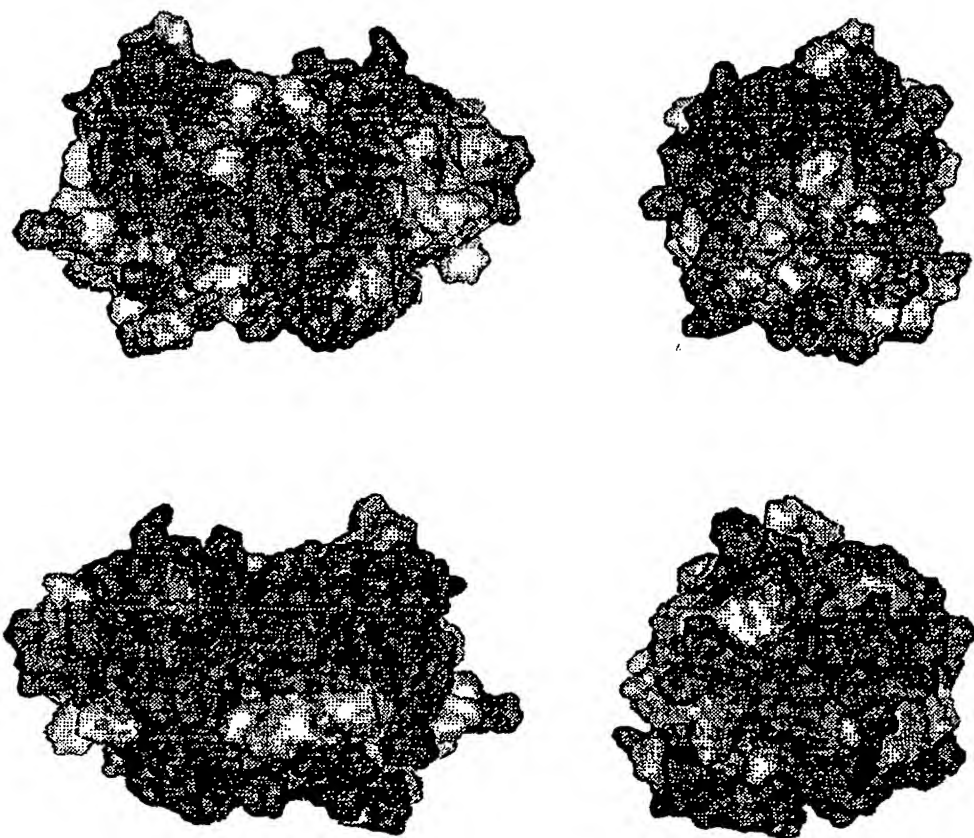


FIG. 36: Der p 1

10001245.11501

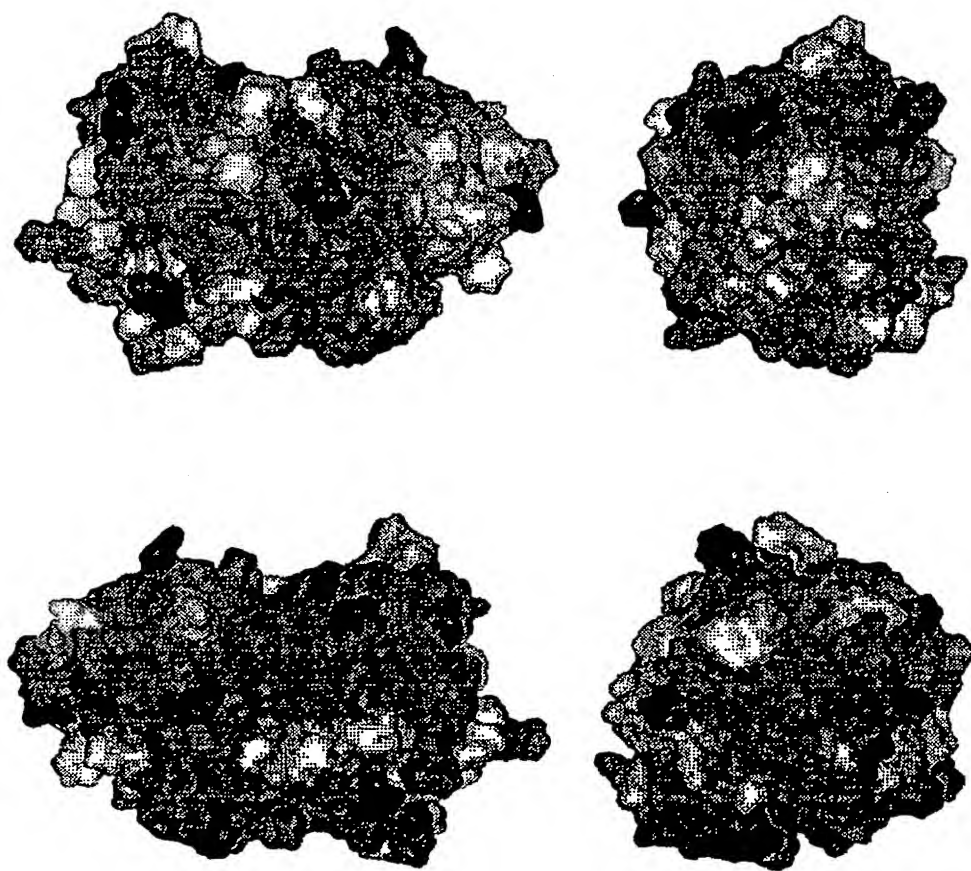


FIG. 37: Der p 1 mutant

2711 2712 2713 2714 2715 2716 2717 2718 2719 2720 2721 2722 2723 2724 2725 2726 2727 2728 2729 2730 2731 2732 2733 2734 2735 2736 2737 2738 2739 2740 2741 2742 2743 2744 2745 2746 2747 2748 2749 2750 2751 2752 2753 2754 2755 2756 2757 2758 2759 2760 2761 2762 2763 2764 2765 2766 2767 2768 2769 2770 2771 2772 2773 2774 2775 2776 2777 2778 2779 2780 2781 2782 2783 2784 2785 2786 2787 2788 2789 2790 2791 2792 2793 2794 2795 2796 2797 2798 2799 2800 2801 2802 2803 2804 2805 2806 2807 2808 2809 2810 2811 2812 2813 2814 2815 2816 2817 2818 2819 2820 2821 2822 2823 2824 2825 2826 2827 2828 2829 2830 2831 2832 2833 2834 2835 2836 2837 2838 2839 2840 2841 2842 2843 2844 2845 2846 2847 2848 2849 2850 2851 2852 2853 2854 2855 2856 2857 2858 2859 2860 2861 2862 2863 2864 2865 2866 2867 2868 2869 2870 2871 2872 2873 2874 2875 2876 2877 2878 2879 2880 2881 2882 2883 2884 2885 2886 2887 2888 2889 2890 2891 2892 2893 2894 2895 2896 2897 2898 2899 2900 2901 2902 2903 2904 2905 2906 2907 2908 2909 2910 2911 2912 2913 2914 2915 2916 2917 2918 2919 2920 2921 2922 2923 2924 2925 2926 2927 2928 2929 2930 2931 2932 2933 2934 2935 2936 2937 2938 2939 2940 2941 2942 2943 2944 2945 2946 2947 2948 2949 2950 2951 2952 2953 2954 2955 2956 2957 2958 2959 2960 2961 2962 2963 2964 2965 2966 2967 2968 2969 2970 2971 2972 2973 2974 2975 2976 2977 2978 2979 2980 2981 2982 2983 2984 2985 2986 2987 2988 2989 2990 2991 2992 2993 2994 2995 2996 2997 2998 2999 3000

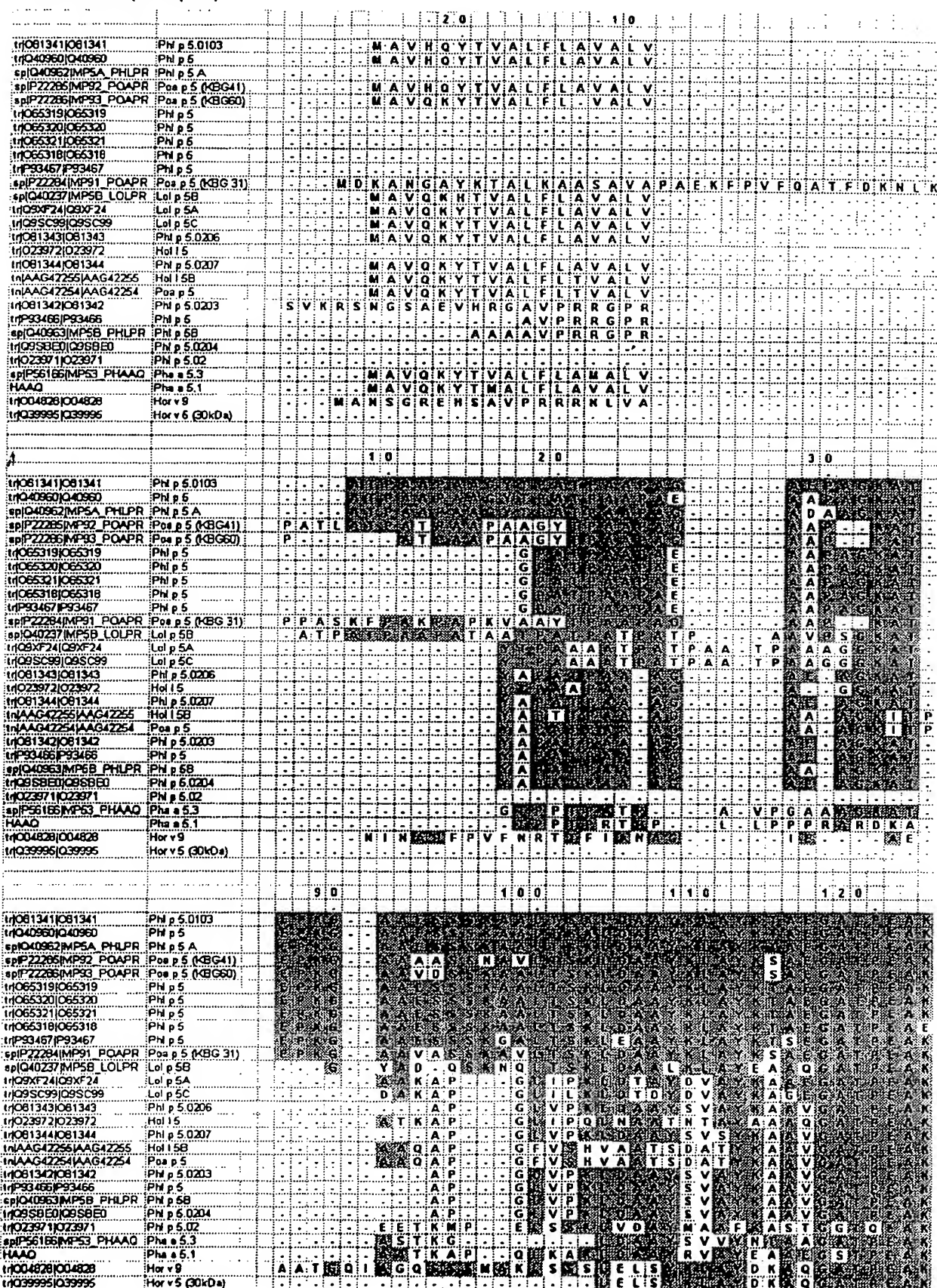
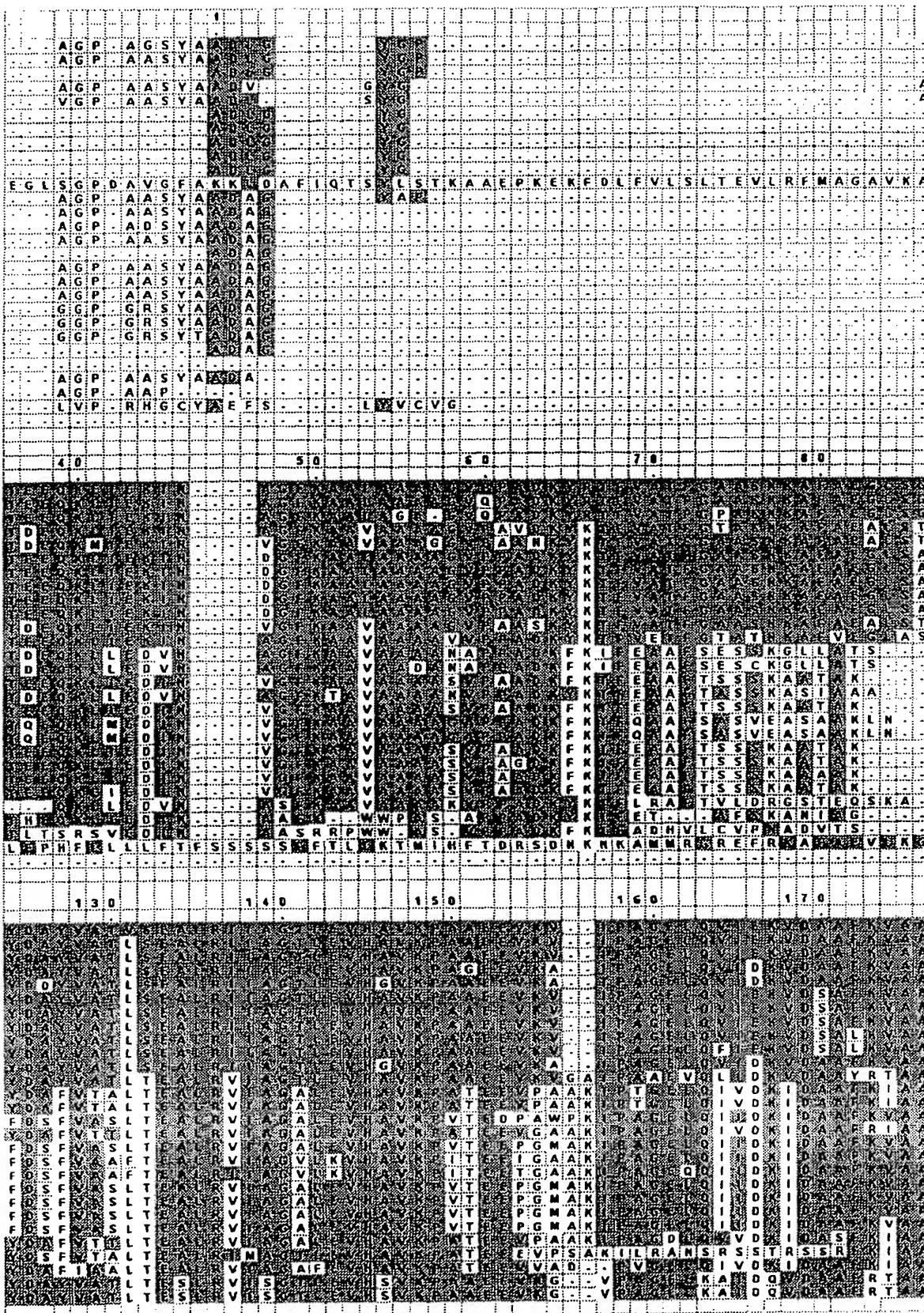
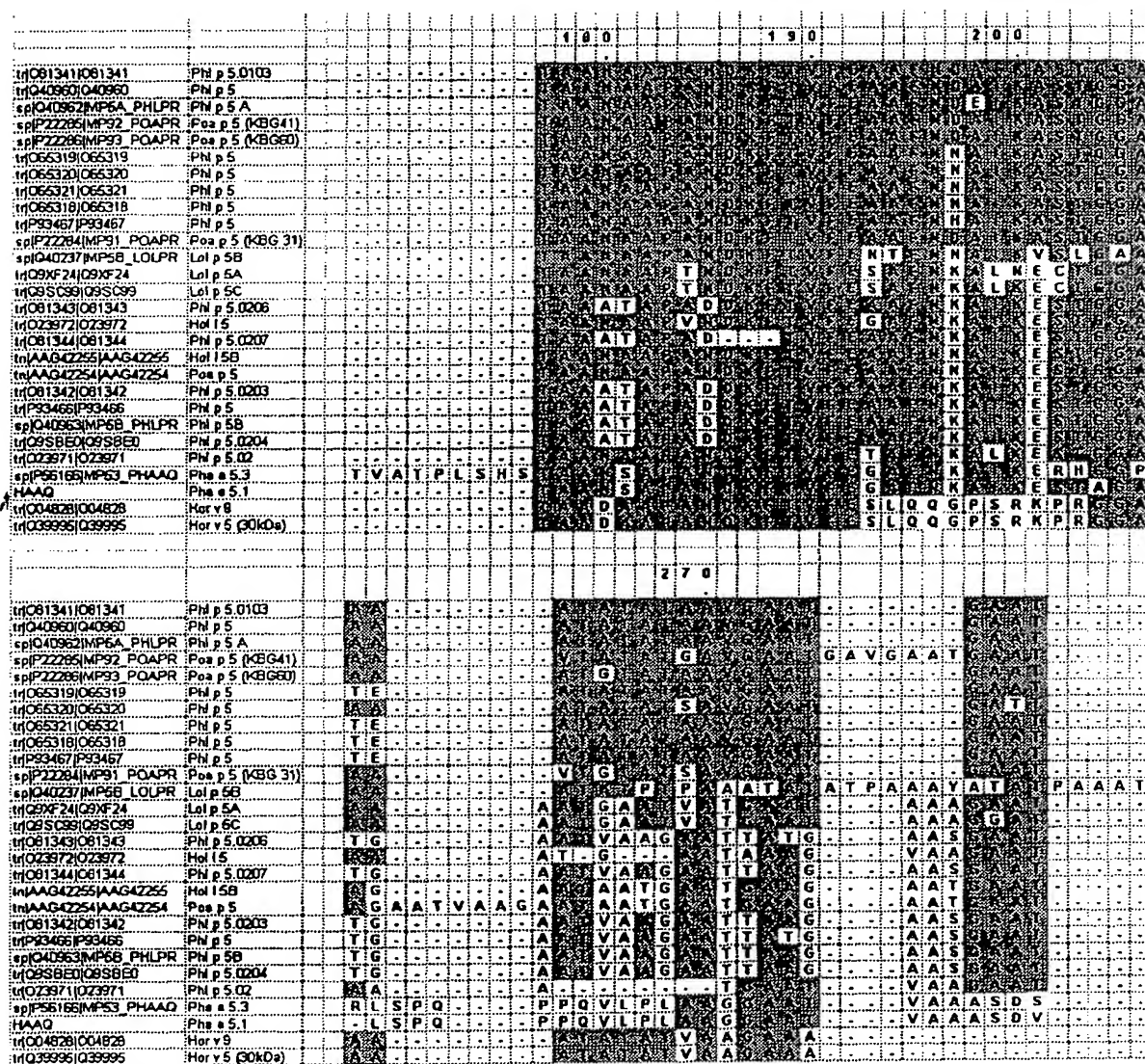


FIG. 38B (Phi p 5)



1000 244 1150

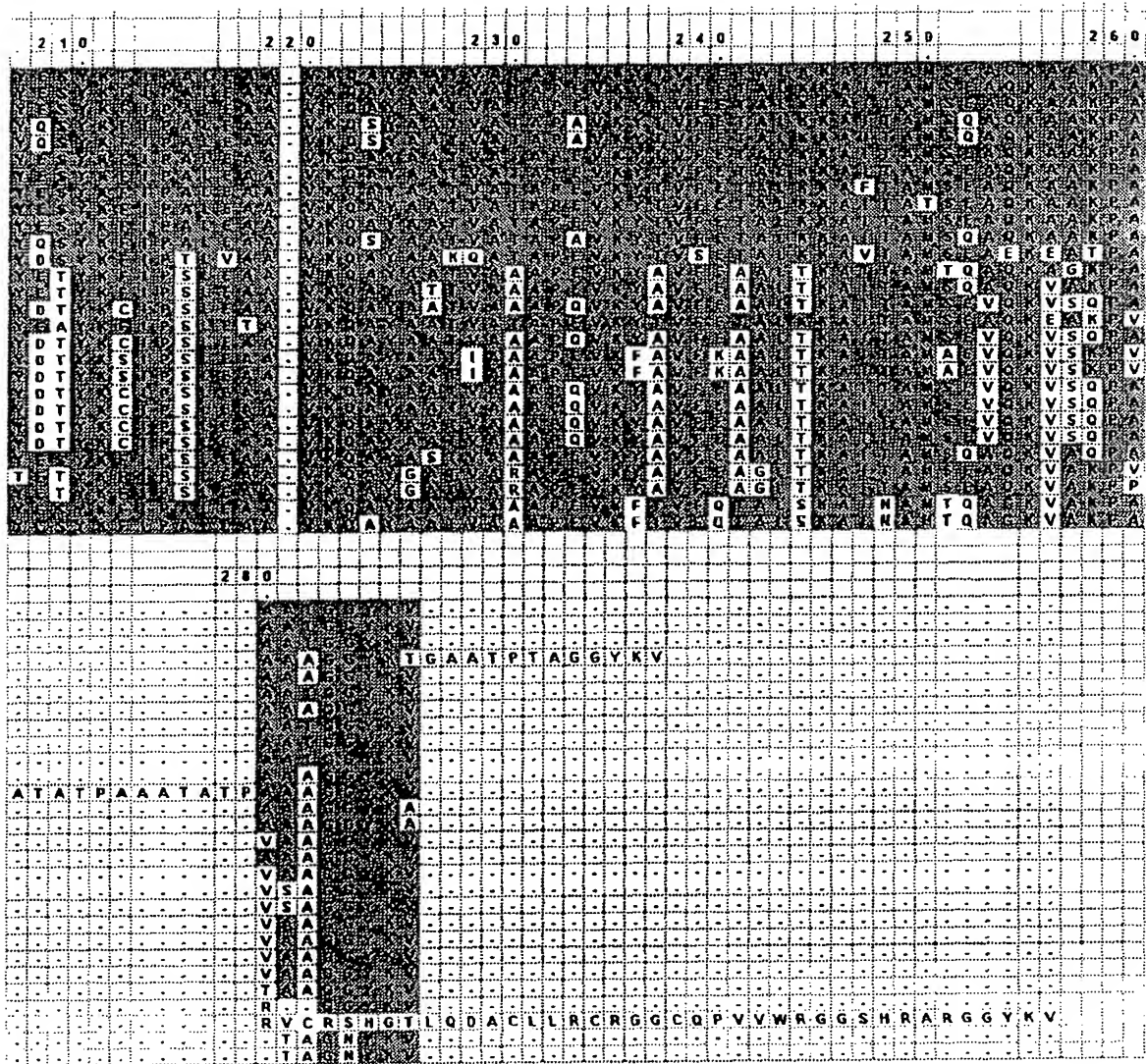
FIG. 38C (Phl p 5)



10001245.114501

FIG. 38D (Phl p 5)

10001245-111501



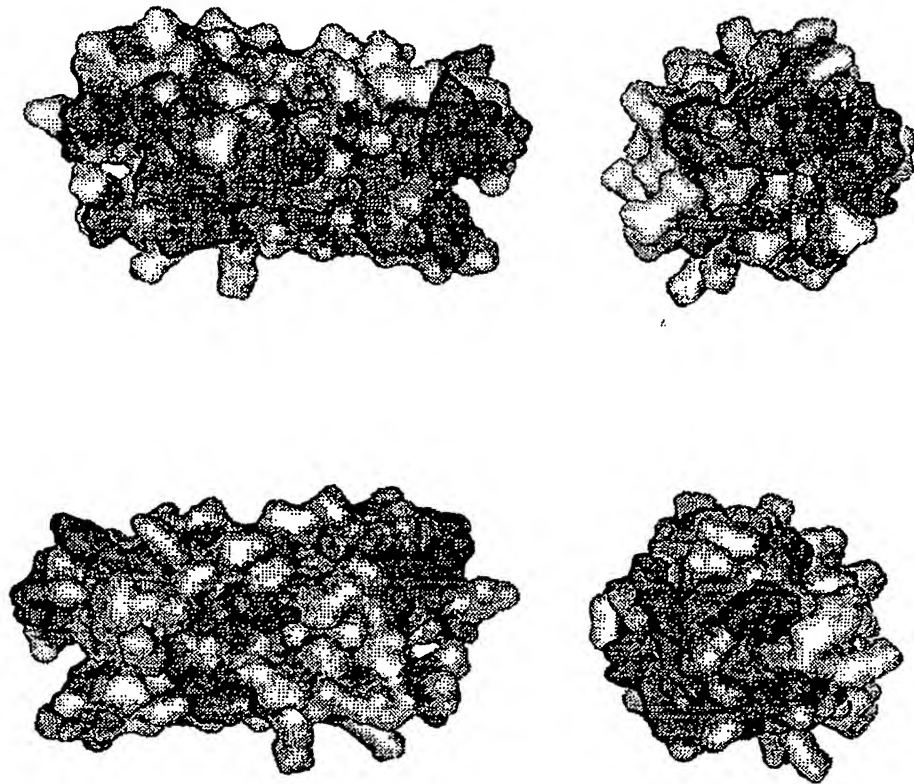


FIG. 39A: Phl p 5, Model A

10003245.11504

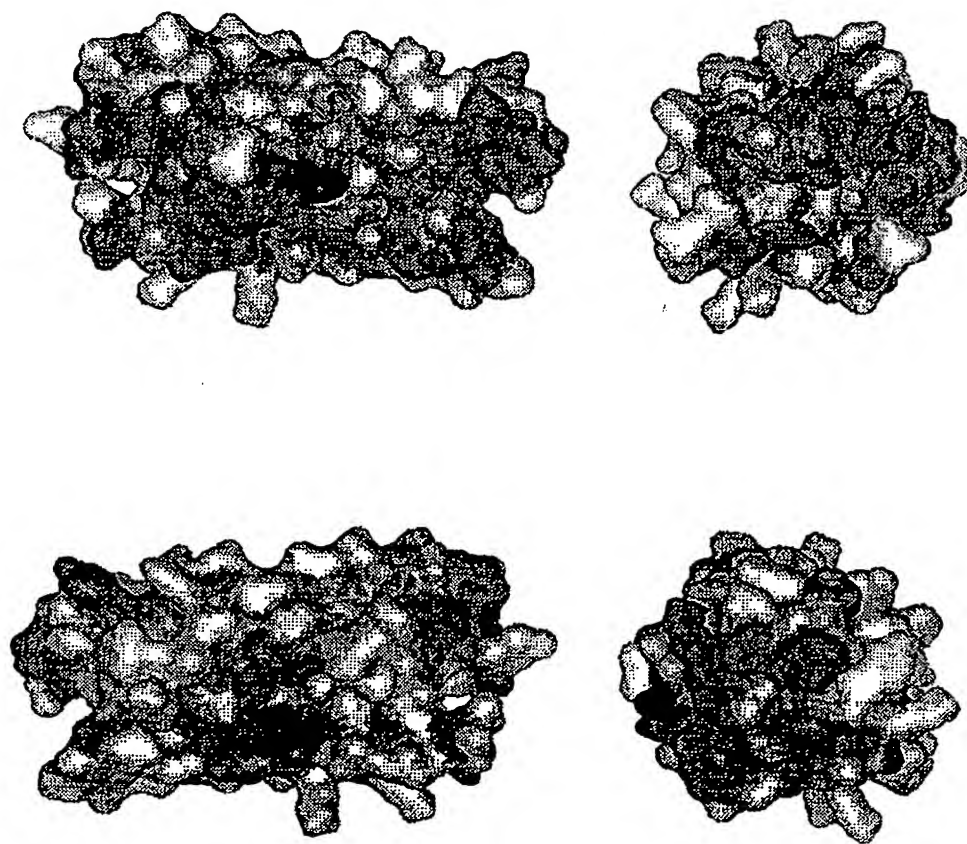


FIG. 40A: Phl p 5 mutant, Model A

1000345-1153

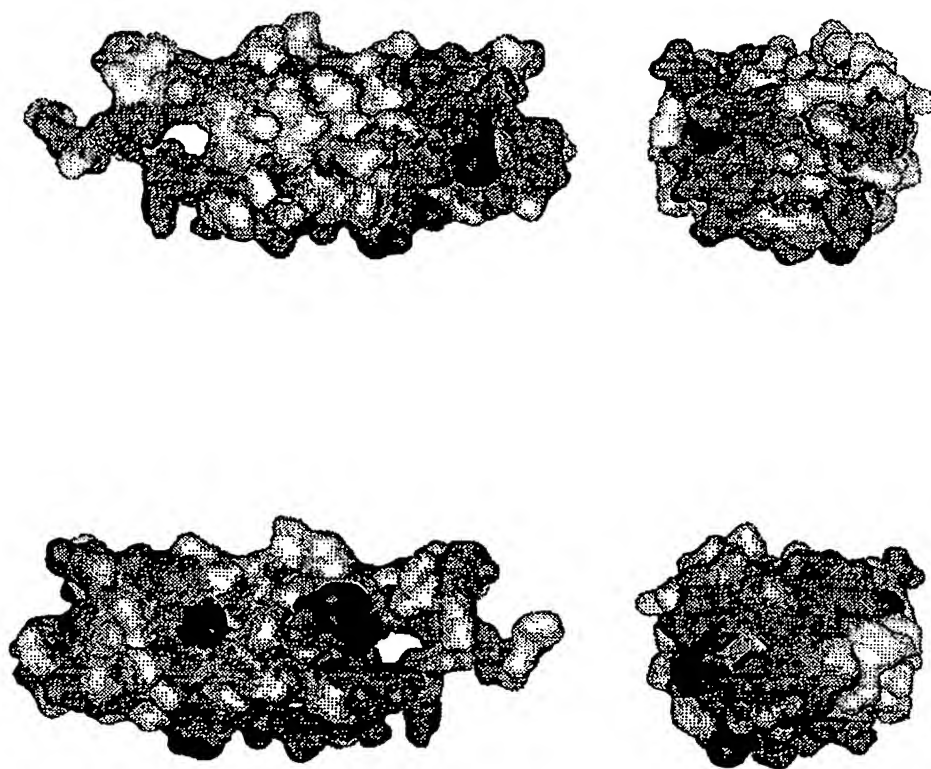


FIG. 40B: Phl p 5 mutant, Model B

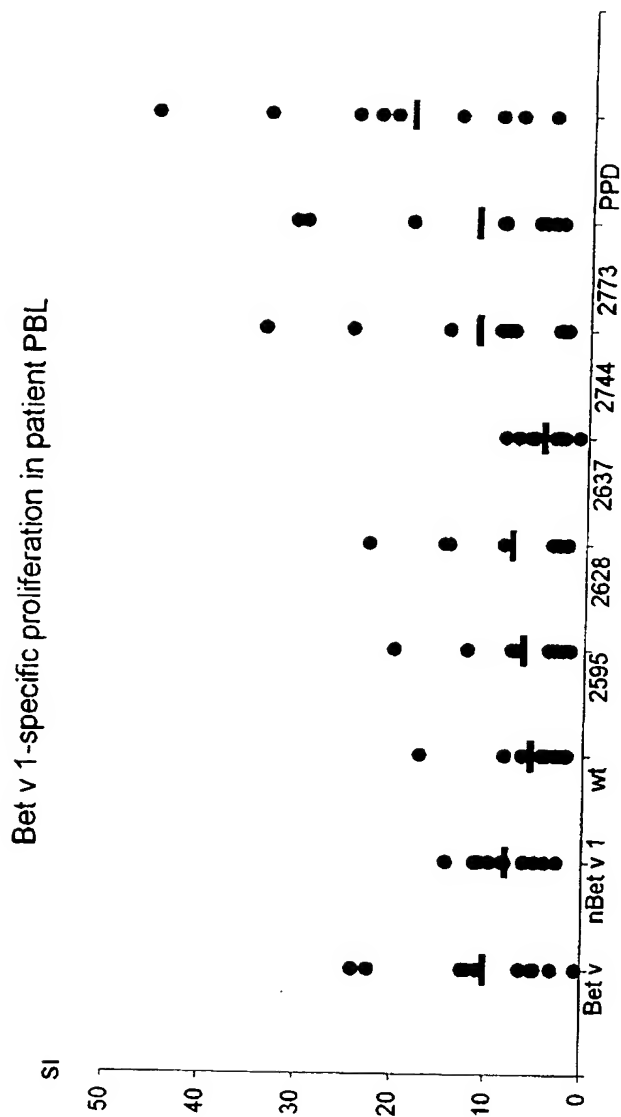


Figure 41: Stimulation of Bet v 1 samples

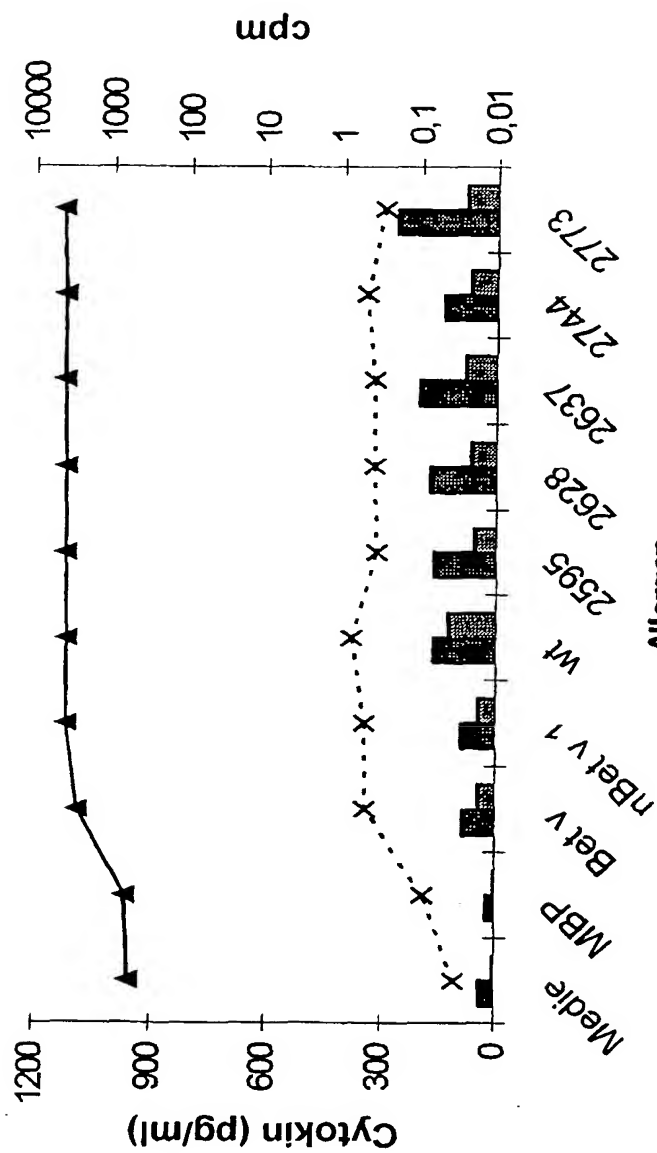
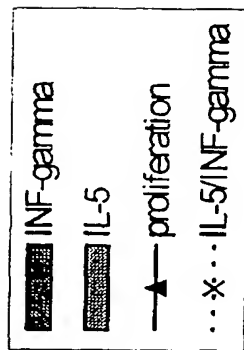


FIG. 42

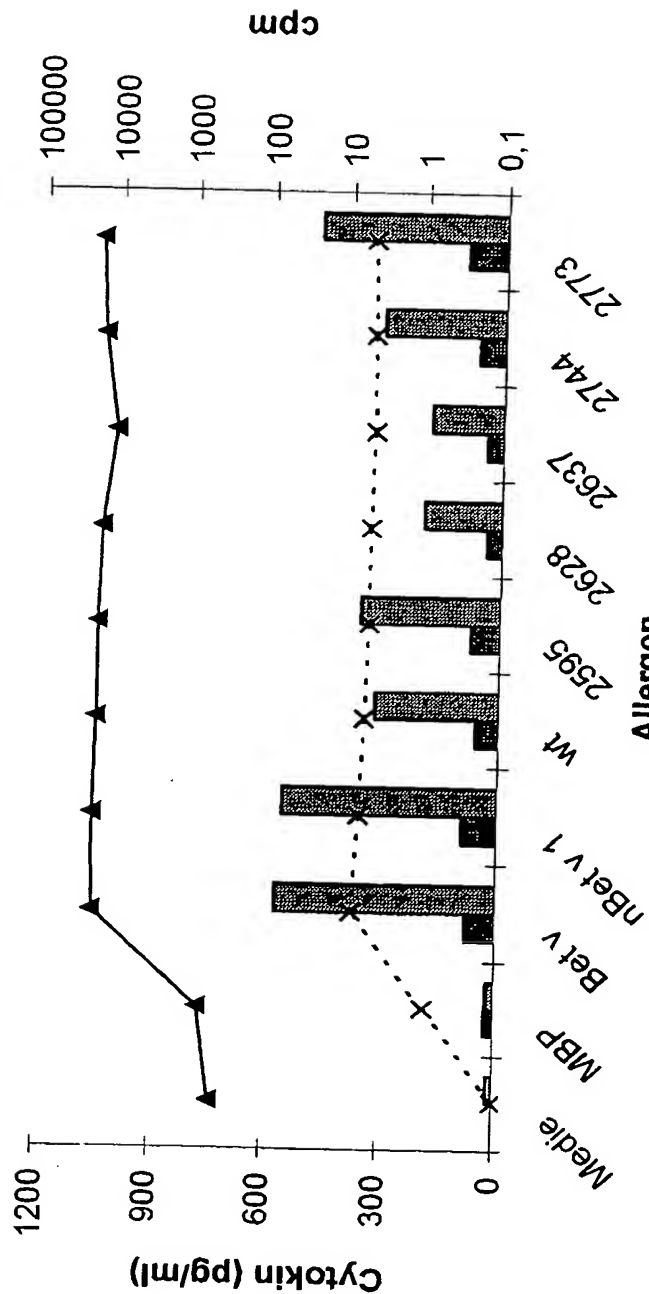
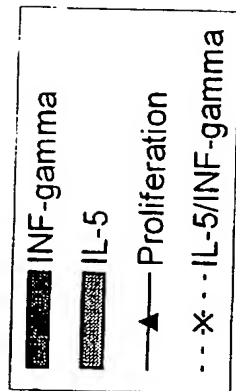


FIG. 44